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Perioperative Brain Injury in Relation to Early Neurodevelopment among Children with Severe Congenital Heart Disease: Results from a European Collaboration

Astrid Neukomm, MD[1*], Nathalie H.P. Claessens, MD, PhD[2-6*], Alexandra F. Bonthrone, PhD[7], Raymond Stegeman, MD, PhD[8,], Maria Feldmann, MD, PhD[1], Maaike Nijman, MD[2-6], Nicolaas J.G. Jansen, MD, PhD[3,8], Joppe Nijman, MD, PhD[3], Floris Groenendaal, MD, PhD[2,6], Linda S. de Vries, MD, PhD[2,6], Manon J.N.L. Benders, MD, PhD[2,6], Johannes M.P.J. Breur, MD, PhD[4], Felix Haas, MD, PhD[5], Mireille N. Bekker, MD, PhD[9], Thushiha Logeswaran, MD, PhD[10], Bettina Reich, MD, PhD[11], Raimund Kottke, MD[12], Hitendu Dave, MD[13], John Simpson, FRCP, MD[14], Kuberan Pushparajah, MRCPCH, MD[7,14], Christopher J. Kelly, MRCPCH, PhD[7], Sophie Arulkumaran, FRCR, PhD[7], Mary A. Rutherford, FRCR, FRCPCH, MD[7], Serena J. Counsell, PhD[7], Andrew Chew, MD[7], Walter Knirsch, MD[15], Maaike C.A. Sprong, PT, MSc [16], Monique M. van Schooneveld, PhD[17], Cornelia Hagmann, MD, PhD[18*], Beatrice Latal, MD, MPH[1*], for the European Association Brain in Congenital Heart Disease (EU-ABC) consortium

* Shared first and last authorship

1 Child Development Center, University Children's Hospital Zurich, Switzerland

2 Department of Neonatology, 3 Department of Pediatric Intensive Care, 4 Department of Pediatric Cardiology, 5 Congenital Cardiothoracic Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht and Utrecht University , the Netherlands

6 Utrecht Brain Center, UMC Utrecht, Utrecht University, the Netherlands

7 Centre for the Developing Brain, School of Biomedical Engineering and Imaging Sciences, King's College London, United Kingdom

8 Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, the Netherlands

9 Department of Obstetrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands

10 Pediatric Heart Center, University Hospital Giessen, Justus-Liebig-University Giessen, Germany

11 Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University of Munich, Germany

12 Department of Diagnostic Imaging, University Children's Hospital Zurich, Switzerland

13 Division of Congenital Cardiovascular Surgery, University Children's Hospital Zurich, Switzerland

14 Pediatric Cardiology Department, Evelina Children's Hospital London, United Kingdom

15 Pediatric Cardiology, Pediatric Heart Center, Department of Surgery, and Children's Research Center, University Children's Hospital, University of Zurich, Switzerland

16 Child Development & Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands

17 Sector of Neuropsychology, Department of Pediatric Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, the Netherlands.

18 Department of Neonatology and Pediatric Intensive Care, University Children's Hospital Zurich, Switzerland

Correspondence:

Beatrice Latal, Child Development Center

University Children's Hospital Zurich

Steinwiesstrasse 75, 8032 Zurich

Email: bea.latal@kispi.uzh.ch

Phone: +41 44 266 79 24

Fax: +41 44 266 71 64

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Disclosures

None.

Abstract

Objective To examine the relationship between perioperative brain injury and neurodevelopment during early childhood in patients with severe congenital heart disease (CHD).

Study design 170 children with CHD and born at term who required cardiopulmonary bypass surgery in the first 6 weeks after birth were recruited from 3 European centers and underwent preoperative and postoperative brain MRIs. Uniform description of imaging findings was performed and an overall brain injury score was created, based on the sum of the worst preoperative or postoperative brain injury subscores. Motor and cognitive outcomes were assessed with the Bayley Scales of Infant and Toddler Development Third Edition at 12 to 30 months of age. The relationship between brain injury score and clinical outcome was assessed using multiple linear regression analysis, adjusting for CHD severity, length of hospital stay (LOS), socioeconomic status (SES), and age at follow-up.

Results Neither the overall brain injury score nor any of the brain injury subscores correlated with motor or cognitive outcome. The number of preoperative white matter lesions was significantly associated with gross motor outcome after correction for multiple testing ($p=0.013$, $\beta=-0.50$). SES was independently associated with cognitive outcome ($p<0.001$, $\beta=0.26$), and LOS with motor outcome ($p<0.001$, $\beta=-0.35$).

Conclusion Preoperative white matter lesions appear to be the most predictive MRI marker for adverse early childhood gross motor outcome in this large European cohort of infants with severe CHD. LOS as a marker of disease severity, and SES influence outcome and future intervention trials need to address these risk factors.

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Congenital heart disease (CHD) represents the most frequent congenital malformation.[1] CHD patients may display cognitive, language, and motor developmental delay during infancy and early childhood.[1, 2] These problems may persist until school age and adolescence, affectiing educational achievement and adult outcome.[3, 4] Preoperatively, brain injury, such as white matter injury (WMI), hemorrhagic injury, and stroke, is evident in 39% of neonates with complex CHD[5] and may increase to 56% postoperatively, in particular among those with univentricular CHD.[6, 7] In the CHD population, existing studies are contradictory in regards to the association between perioperative brain injuries and subsequent neurodevelopmental outcome. Some studies have found an association of neonatal brain injury with neonatal neurological abnormalities,[8] lower cognitive performance at 1 year of age,[9] worse cognitive and motor development at 2 years of age,[10, 11] and poorer cognition at 6 years of age.[11] In contrast, another large study found no association between brain injury and 2-year outcome.[12] Potential reasons for the inconsistent association between brain injury and outcome is a lack of common definition of the severity of brain injuries as well as a largely varying prevalence of brain injury between different centers due to methodological differences around inclusion criteria, surgical and perioperative management, and MRI protocols.[7, 13]

The aim of our study was to investigate the relationship between perioperative overall brain injury load and developmental outcome at 12 to 30 months of age in a pooled cohort of CHD patients from 3 European centers, who required cardiopulmonary bypass surgery in the first 6 weeks after birth. To measure the overall brain injury load, we evaluated preoperative and postoperative imaging according to our previously published standardized description of brain injuries[7] and we created an overall brain injury score considering type and location of preoperative and postoperative brain injuries. We hypothesized that a higher overall brain injury score was associated with worse neurodevelopmental outcome within the first two years.

Methods

Study Design and Sample

Three prospective observational cohort studies were combined within European Association Brain in Congenital Heart Disease (EU-ABC-) consortium as described in detail in previous reports.[7, 14] Neonates with CHD who underwent cardiac surgery during the first 6 weeks after birth at Wilhelmina Children's Hospital Utrecht (WKZ 2016-2019), University Children's Hospital Zurich (UCZ 2009-2019), and St Thomas' Hospital London (KCL 2014-2019) and who had a preoperative and/or postoperative MRI were eligible for inclusion. CHD included in the study were transposition of the great arteries (TGA, with or without arch obstruction), single ventricle physiology (SVP) defined as hypoplastic left heart complex and hypoplastic right heart complex, and left ventricular outflow tract and/or aortic arch obstruction (LVOTO), which was defined as left ventricular outflow tract and/or aortic arch obstruction such as aortic valve stenosis, or aortic arch coarctation, hypoplasia, or interruption. Children with known or suspected genetic or syndromic disorders were excluded. Clinical characteristics were collected prospectively at each center. The respective institutional ethical research committees approved the studies (WKZ, No. 16-093; UCZ KEK StV-23/619/04; KCL 07/H0707/105). Parental informed consent was obtained for the use of clinically obtained data for research purposes (WKZ) or prior to study enrollment (UCZ, KCL). The STROBE guidelines for reporting observational studies were followed.[15]

Brain MRI Protocol

Brain MRI was performed preoperatively and/or postoperatively according to clinical (WKZ) or research study (UCZ, KCL) protocol. All neonates underwent a 3-Tesla brain MRI. MRI system, head-coil, scanning procedures, and protocols were described in detail previously.[7] All neonates underwent T1, T2, diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI). Neonates in WKZ and KCL also underwent MR venography (MRV).

Brain Injury Scoring

MRI scans from each cohort were assessed using a uniform description of brain imaging findings as described in a previous report from the EU-ABC consortium.[7] For this study, a brain injury score was developed based on a combination of different brain injury severity gradings used in preterm research.[16-19] This score is shown in **Figure 1**. Briefly, the system consists of three subscores: hemorrhagic injury (score 0-3), punctate white matter injury (WMI, score 0-3), and stroke (score 0-3). The preoperative sum score represents the sum of all preoperative subscores (score 0-9); the postoperative sum score represents the sum of all corresponding postoperative subscores (score 0-9). The worst subscore represents the highest score obtained within a subscore either preoperatively or postoperatively (score 0-3). The overall brain injury score indicates the brain injury load and is the sum of the worst subscores, either on preoperative or postoperative imaging (score 0-9). In addition, absolute WMI volume in cubic millimeters was segmented and calculated on 3D T1 images using ITK-SNAP (www.itksnap.org) (KCL) or 3D Slicer (http://www.slicer.org) (WKZ, UCZ) on preoperative and postoperative imaging.

Outcome Measurements

All children underwent motor and cognitive assessment using the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III). At UCZ, children were assessed at 12 months or 24 months. At KCL, children were assessed at 24 months. At WKZ, children were assessed at 18 months for motor development and at 30 months for cognition. The Bayley-III cognitive and motor composite scores (mean 100, SD 15) and fine and gross motor scaled scores (mean 10) were used. In one center, language composite scores were not collected and therefore we did not use this outcome variable. The raw scores for each child were transformed into scaled scores using the American norms. For all children, the presence of cerebral palsy at the time of assessment was noted.

Socioeconomic Status

We used the degree of maternal education as a proxy of socioeconomic status (SES) and classified it as low, middle, or high SES using country specific scoring systems.

Statistical Analysis

Analyses were performed using R (version 4.1.0, The R Foundation, Vienna, Austria). Neurodevelopmental outcome was compared with the normative mean using one-sample t-tests and Mann-Whitney U tests depending on distribution of data. For the primary research question (association between overall brain injury score and outcome), a multiple linear regression analysis was used, controlling for CHD subgroup (TGA, SVP, and LVOTO with LVOTO as the reference), length of hospital stay (LOS; defined as duration between birth and discharge to home), SES; age at follow-up, and center (Utrecht, Zurich, London with London as the reference). Number of surgeries until follow-up was highly correlated with LOS ($p<0.001$) and therefore only LOS was included in further analyses. There were no other significant collinearities. LOS was log-transformed due to skewed data distribution. Cognitive outcome was controlled for SES.[1] Missing values for SES (n=5) were imputed using the "mice" package in R.[20]

The following secondary models were calculated: The overall brain injury score (BIS) was dichotomized into no brain injury to mild brain injury (BIS 0-4) versus moderate to severe brain injury (BIS ≥5) and the cognitive and motor outcome was dichotomized into <85 versus ≥85. Linear regression models were used to correlate the dichotomized overall brain injury score with outcome. Using logistic regression models, association between the dichotomized outcome and injury scores were estimated. Interaction models between brain injury scores and SES were calculated to evaluate the association with cognition. The association between brain injury scores and outcome was assessed for patients who had only one cardiac surgery. The relationships between the number of WM lesions and the WMI-volume-to-total-brain-volume ratio (calculated in %) with outcome were assessed respectively using multiple linear regression models for children who had a WM lesion. All these models were adjusted for the same variables as mentioned above (CHD subgroup, LOS, SES, age at follow-up, and center for all models). To address multiple testing, Benjamini-Hochberg correction was applied separately

for number of tested brain injury scores within the primary analysis models, within secondary analysis models, and for number of tested WMI variables (number of WMI lesions and WMI-volume-to-total-brain-volume ratio preoperatively and postoperatively).[21]

Results

Participant Characteristics

Demographic, neonatal, and follow-up characteristics are presented in **Table I**. A total of 202 children from3 European centers (London: 51; Utrecht: 79; Zurich: 72) were included in this study (Table I). 12 children died, and 5 children were excluded due to suspected or proven genetic comorbidity or genetic syndrome. Of the remaining 185 children, 166 children underwent cognitive testing (follow-up rate 90%); 3 children underwent assessment with a different test than the Bayley-III due to age at assessment. 169 children underwent motor assessment (follow-up rate 91%); one child was sick during the testing and was not included in this analysis. (**Figure 2**)

Neurodevelopment

Median age at the cognitive follow-up was 23.0 months (IQR 13.5 to 29.0 months) and 19.0 months (IQR 14.0 to 22.2 months) at the motor follow-up. Overall, the mean outcome parameters of the sample were within the normal range when compared with normative test means (**Table I**). There was no association between age at follow-up and neurodevelopmental outcome (see Table II). A cognitive composite score below 85 was seen in 11 children (6.7%), and in one child (0.6%) the cognitive score was below 70. Twenty-three (13.7%) children had a motor composite score below 85, and two children (1.2%) had a motor composite score below 70. Thirty-six (21.4%) children had a gross motor scaled score below 7, and 5 (3.0%) children had a fine motor scaled score below 7. Two (1.2%) children had cerebral palsy at the time of follow-up (one with a hemiparesis due to a preoperative middle cerebral artery stroke, another due to a severe global hypoxic-ischemic brain injury postoperatively). LOS was significantly associated with motor outcome (**Table II**) ,adjusting for overall brain injury severity, CHD type, SES, age at follow-up, and center.

Load of Brain Injury and Outcome

The distribution of the brain injury score is shown in **Figure 3**. The overall brain injury score and all other subscores including preoperative and postoperative imaging did not correlate with either cognitive or motor outcome (**Tables II and III)**. When the overall brain injury score was dichotomized into no or mild brain injury (defined as score 0 to 4; n = 162 patients [95.3%] of which 74 children [43.5%] had no brain injury on MRI) and into moderate to severe brain injury (defined as score ≥5; n = 8 patients [4.7%}), it was still not associated with outcome (cognition: B=-5.53, SE B=5.01, β=-0.08, t=-1.105, p=0.27, corrected p=; motor outcome: B=-3.49, SE B=4.26, β=-0.06, t=-0.82, p=0.41, corrected p=0.41). When outcome was dichotomized (<85 versus ≥85) neither overall brain injury score nor any other brain injury subscore was associated with outcome (data not shown). Of the total sample, 127 patients (74.7%) had undergone only one cardiac surgery until the time of follow-up (95 TGA, 31 LVOTO, 1 SVP); there was no significant relationship between the overall brain injury score and all other brain injury subscores with outcome in these infants (data not shown).

Number and Volume of WMI and Outcome

The number of preoperative WM lesions was associated with motor outcome, and this remained significant after multiple testing (**Table IV** and **Figure 4**). *Post hoc* analysis showed that number of preoperative WM lesions were associated only with gross motor outcome (B=-0.26, SE B=0.08, β=-0.52, t=-3.42, p=0.002, adjusted R^2=0.31) but not with fine motor outcome (B=-0.15, SE B=0.28, β=-0.08, t=-1.79, p=0.08, adjusted R^2=0.25). Neither number nor volume of postoperative WM lesions, nor volume of preoperative WM lesions correlated with motor or cognitive outcome.

Socioeconomic Status and Neurodevelopmental Outcome

SES was significantly associated with cognitive outcome (**Table II**). We did not find an interaction of SES with overall brain injury score nor any brain injury subscore on cognitive outcome (data not shown).

Discussion

This study investigated the association between neonatal preoperative and postoperative brain injury on MRI and neurodevelopment within the first 2 years of life in a large multicenter European cohort of children with severe CHD. The number of preoperative punctate WM lesions was associated with motor functioning, especially gross motor functioning, at the age of 12 to 30 months. However, neither the overall brain injury score nor any other injury subscore was associated with neurodevelopmental outcome.

Several studies have shown the presence of perioperative brain injuries in newborns undergoing open-heart surgery for severe CHD.[5, 7, 8, 10-13, 22-29] These studies report a wide range of brain injury prevalence, depending on the study sample, timing of MRI, and other factors.[5, 30] However, it is difficult to compare prevalence findings between studies due to a historical lack of standardized imaging protocols and brain injury scoring systems in CHD.[7] To examine the impact of brain injuries on neurodevelopment in this study, we used our recently developed standardized description of preoperative and postoperative cerebral MRI findings[7] and here report a new brain injury score. Although we have a high incidence of reported brain injuries in this cohort (56.5% of the 170 participants had evidence of perioperative brain injury) compared with previous studies,[8, 26, 31-33] the severity of brain injury was low with only 4.7% of patients having moderate to severe brain injury.[26, 31] Many studies using different scanning protocols and scoring systems of cerebral MRI findings report a lower incidence of brain injury.[8, 26, 31-33] This may suggest that our scoring system captures more subtle brain injuries compared with others.

There is conflicting literature on the association between neonatal cerebral MRI findings and early neurodevelopmental outcome.[9-11, 34-38] Some studies did not show an impact of perioperative neonatal brain injury on neurodevelopmental outcome.[35, 37, 38] However, in this study, a significant association between number of preoperative WM lesions and gross motor functioning was found. These findings are in line with previous studies including Stegeman et al, who reported an association of WMI with worse gross motor development at 9 months of age in a heterogenous cohort of CHD children with a rate of 45% of patients with moderate to severe

postoperative WMI.[34] Similarly, Peyvandi et al found worse motor outcome in 41% of CHD children with moderate to severe WMI in comparison with children with no or mild WMI at 12 and 30 months of age.[10] WMI volume was likewise associated with outcome.[10]

Claessens et al demonstrated an association between neonatal moderate to severe perioperative WMI and lower full-scale IQ in children with aortic arch obstruction aged 6 years.[11] This cohort showed a rate of 62% of patients with moderate to severe WMI.[11] Other studies did not investigate WMI separately but correlated an overall brain injury score with neurodevelopmental outcome. An association of preoperative brain injury including WMI, stroke, and hemorrhage with motor and language development at 12 months has been reported[39] as well as a correlation between postoperative brain injury and poorer cognitive development at 12 months of age.[9] Our study supports the findings that WMI might be the type of injury with the greatest impact on gross motor outcome.

WMI is the most prevalent brain injury type before and after neonatal cardiopulmonary bypass surgery in the neonatal CHD population.[7] In a previous study of the EU-ABC collaboration on the same cohort,[14] induced vaginal delivery and balloon atrial septostomy increased the risk of preoperative WMI. SVP and younger postoperative gestational age were risk factors for new postoperative WMI.[14] WMI is associated with periods of reduced brain perfusion due to the type of CHD and due to immature autoregulatory mechanisms lacking the ability to cope with hemodynamic fluctuations.[40] Such reduced perfusion can lead to oxidative stress and apoptotic cell death of immature WM cells.[41, 42] Two additional factors predispose the developing WM to injury from hypoxia-ischemia: the presence of arterial end and border zones in the periventricular region,[43] and a propensity for the critically ill neonate to exhibit a pressure-passive circulation related to a disturbance of cerebral auto-regulation. These mechanisms may contribute to the typical finding of reduced and injured WM in CHD neonates.[44] Furthermore, prenatal hypoxia delays fetal brain development[45, 46] leading to increased susceptibility of the WM to brain injury.[12, 26, 36, 47] There is a spatial predilection for the occurrence of WMI in CHD patients that matches the expected maturation of pre-oligodendrocytes.[48] A higher load of WMI might indicate more diffuse affected WM axons.[49] This could suggest that overall, more diffuse

damage of the WM axons leads to altered brain development rather than the visible WMI itself. A recent study in neonates with CHD showed that WMI leads to abnormal structural connectivity and that the level of neonatal structural connectivity was a prognostic marker for early motor development.[50] Another study underscores these findings with no correlation between overall brain injury and neurodevelopment but reported an association between brain development at 3 months of age and neurodevelopment at 2 years of age.[12]

In this study, the number of preoperative WM lesions was significantly associated with gross motor outcome after adjusting for confounders such as SES and after correction for multiple testing. This is consistent with reports in children born preterm looking at prediction of motor outcome based on the number and location of punctate WM lesions.[17, 51] It was shown, that a high number of WM lesions and lesions involving the corticospinal tracts were associated with poorer motor outcome.[17] In addition, altered WM microstructure adjacent to the punctate WM lesions could be found in neonates with a higher load of punctate WMI.[52] This pattern of number of punctate WMI and motor outcome seems similar in preterm children as in our children with CHD. We have recently also shown that in neonates with CHD, larger WMI volume was associated with lower network strength and global efficiency[53] suggesting a widespread effect of focal WMI on brain development. The association between postoperative lesions and neurodevelopmental outcome in this cohort did not show any significance but rather a trend; this could be explained by the size of the cohort and/or by the larger influence of other risk factors for adverse outcome such as length of hospital stay and socioeconomic status.

Children with severe CHD are at increased risk of impaired neurodevelopment in many domains including motor, cognition, behavior, and executing functioning.[54] The variation in outcome scores between studies likely reflect a difference in inclusion criteria, timing, and methods of neurodevelopmental testing. In our study neurodevelopmental testing was performed at the age of 12 to 30 months, a wide range of testing age due to different follow-up strategies between European sites. Our cohort showed relatively favorable outcomes with most children scoring within the normal range for motor and cognitive development. In part of the European centers that participated in this study, physical therapy – when required – in the first years of

life is standard intervention for children with severe CHD who show any motor developmental delay. We thus cannot exclude that early motor intervention reduced the effect of neonatal brain injury on follow-up motor outcomes. Regarding the relatively high cognitive scores, 3 factors might play a role. Firstly, the average SES in our cohort is higher than expected in the normal population. Secondly, all centers assessed cognitive development using the third edition of the Bayley, which generates rather high cognitive results compared with the second edition and probably overestimates the cognitive functioning of these children.[55] Thirdly, with increasing age when cognition can be tested in more detail and societal demands on children increase, problems in the other domains of cognition, by example executive functioning and/or in behavior may become clearer.[56]

This study has limitations worth mentioning. Firstly, this multicenter study includes cohorts with different inclusion criteria, which might influence our results. The most important differences in patient inclusion were research versus clinical MR scanning, logistics to perform MRI in all severely ill children, CHD type, and different age at follow-up. We are currently working on a prospective database with aligned protocols. Secondly, not all patients have preoperative and postoperative MRI. We tried to account for this limitation by calculating a preoperative, a postoperative, and an overall brain injury score. Third, only a small subgroup of patients showed severe brain injury (4.7%) or severe motor (1.2%) or cognitive (0.6%) delay which may reduce the power to detect associations between these two variables. Fourth, the high proportion of patients with d-TGA compared with more severe cardiac lesions such as SVP likely contributes to the relatively high neurodevelopmental outcomes in this cohort. Fifth, the multicentric approach leads to variability in brain protective techniques during surgery adding to the variability between surgeons. Sixth, the three participating countries have different education systems and thus each country used a different scoring system for the SES.

This multicenter European study shows the impact of preoperative neonatal white matter injury on gross motor outcome in children with severe CHD using a standardised approach in de-

scribing brain injuries. This finding reinforces the diagnostic and prognostic value of conventional neonatal cerebral MRI. Neuroimaging and neurodevelopmental guidelines need to be developed to identify infants who benefit from early developmental interventions.

Abbreviations: Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III); brain injury score (BIS); congenital heart disease (CHD); European Association Brain in Congenital Heart Disease (EU-ABC) consortium; King's College London (KCL); magnetic resonance imaging (MRI); length of hospital stay (LOS); left ventricular outflow tract and/or aortic arch obstruction (LVOTO); socioeconomic status (SES); single ventricle physiology (SVP); transposition of the great arteries (TGA); University Children's Hospital Zurich (UCZ); Wilhelmina Children's Hospital Utrecht (WKZ); white matter injury (WMI); white matter (WM).

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Figure 1. (A) Definition of overall brain injury score and worst entity scores. **(B)** Definition of preoperative and postoperative sum scores.

Figure 2. Flow chart of enrollment.

Figure 3. Histogram of overall brain injury score.

Figure 4. (A) Association of preoperative WMI lesion number with Bayley cognitive composite score (corrected p^a=0.07) **(B)** Association of preoperative WMI lesion number with Bayley motor composite score (corrected p^a=**0.01***) (**C**) Association of the ratio of WMI volume to TBV with Bayley motor composite score (corrected p^a=0.07). WMI, white matter injury; TBV, total brain volume. [a]Benjamini-Hochberg correction for number of tested WMI variables.

Table 1. Neonatal, MRI, and follow-up characteristics of patients with CHD, listed by site.

Number of patients = 170	KCL n= 38 (22.4%)	WKZ n= 63 (37.1%)	UCZ n= 69 (40.6%)
Gestational age, weeks (mean]SD])	38.6 (1.1)	39.4 (1.4)	39.3 (1.1)
Birth weight, g (mean [SD])	3120.9 (428.6)	3379.7 (586.4)	3345.4 (465.2)
Male sex (%)	21 (55.3)	40 (63.5)	50 (72.5)
CHD subgroup (%)			
Left ventricular outflow tract obstruction	11 (28.9)	17 (27.0)	10 (14.5)
Single ventricle physiology	2 (5.3)	15 (23.8)	7 (10.1)
Transposition of the great arteries	25 (65.8)	31 (49.2)	52 (75.4)
Balloon atrioseptostomy (%)	12 (31.6)	20 (31.7)	32 (46.4)
Age at surgery, days (median [IQR])	12.0 [7.0, 16.0]	7.0 [5.0, 10.5]	11.0 [9.0, 14.0]
Cardiopulmonary bypass duration, min (median [IQR])	148.0 [60.8, 187.0]	153.0 [130.0, 183.5]	174.0 [136.0, 209.2]
Hospital stay, days (median [IQR])	22.5 [17.2, 29.0]	22.0 [16.5, 38.0]	30.0 [24.0, 40.0]
Age at preoperative MRI, days (median [IQR]) [a]	5.0 [3.0, 7.0]	4.0 [2.2, 6.0]	7.0 [5.2, 8.0]
Age at postoperative MRI, days (median [IQR]) [a]	28.5 [18.8, 42.8]	15.0 [12.5, 19.5]	26.0 [21.0, 33.5]
Overall worst brain injury score (0-9) (median [IQR])	1.0 [0.0, 2.0]	2.0 [1.0, 3.0]	0.0 [0.0, 1.0]
Worst hemorrhage score (0-3) (median [IQR])	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]
Worst WMI score (0-3) (median [IQR])	0.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.0 [0.0, 1.0]

Worst stroke score (0-3) (median [IQR])	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
Preoperative sum score (0-9) (median [IQR]) [a]	0.0 [0.0, 2.0]	0.5 [0.0, 1.0]	0.0 [0.0, 1.0]
Postoperative sum score (0-9) (median [IQR]) [a]	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.0 [0.0, 1.0]
Age at cognitive follow-up, months (median [IQR])	23.0 [22.0, 24.8]	31.0 [27.8, 33.0]	13.0 [12.0, 16.0]
Age at motor follow-up, months (median [IQR])	23.0 [22.0, 24.8]	19.0 [18.0, 20.0]	13.0 [12.0, 16.0]
Socioeconomic status (median [IQR])	2.0 [2.0, 3.0]	3.0 [2.0, 3.0]	2.0 [2.0, 3.0]
Number of cardiac surgeries until follow-up (median [IQR])	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
Cerebral palsy at follow-up (%)	0 (0.0)	1 (1.6)	1 (1.5)
Bayley-III Cognitive Composite Score (mean (SD))	93.7 (10.2)	107.7 (12.9)	104.6 (14.2)
Bayley-III Motor Composite Score (median [IQR])	95.5 [91.0, 102.2]	103.0 [97.0, 110.0]	94.0 [85.0, 103.0]
Bayley-III Fine Motor Scaled Score (median [IQR])	10.0 [8.0, 11.8]	12.0 [11.0, 13.0]	10.0 [9.0, 11.0]
Bayley-III Gross Motor Scaled Score (median [IQR])	9.0 [8.0, 9.0]	9.0 [7.0, 10.0]	8.0 [6.0, 9.0]

Note. CHD, congenital heart disease; IQR, interquartile range; KCL, St Thomas' Hospital London; MRI, magnetic resonance imaging; SD, standard deviation; UCZ, University Children's Hospital Zurich; WKZ, Wilhelmina Children's Hospital Utrecht; WMI, white matter injury. Data are reported as mean and SD for normally distributed data and as median and IQR for non-normally distributed data. Categorical data are reported as numbers and proportions. [a] >10% of data are missing.

Table II. Predictors of cognitive and motor outcome; multiple linear regression models.

Dependent variable	Independent variable	B	SE B	β	t	p	Corrected p[a]	Adjusted R^2	p of whole model
Cognitive CS	Overall BIS	-0.456	0.686	-0.048	-0.665	0.507	0.634	0.288	**<0.001*** **
	SVP	-3.305	3.586	-0.084	-0.922	0.358			
	TGA	2.803	2.346	0.098	1.195	0.234			
	Hospital stay (log)	-2.480	1.935	-0.109	-1.282	0.202			
	SES	3.400	1.384	0.170	2.456	**0.015***			
	Age at follow-up	-0.704	0.204	-0.410	-3.454	**0.001****			
	Utrecht	19.957	2.934	0.684	6.801	**<0.001*** **			
	Zurich	5.582	3.016	0.199	1.851	0.066			
Motor CS	Overall BIS	-0.544	0.647	-0.064	-0.841	0.402	0.634	0.197	**<0.001*** **
	SVP	-4.524	3.440	-0.123	-1.315	0.190			
	TGA	1.245	2.275	0.047	0.547	0.585			
	Hospital stay (log)	-5.963	1.861	-0.281	-3.203	**0.002****			

SES	2.418	1.317	0.131	1.836	0.068
Age at follow-up	0.083	0.229	0.034	0.362	0.718
Utrecht	8.234	2.739	0.307	3.006	**0.003****
Zurich	1.249	3.131	0.048	0.399	0.691

Note. B, unstandardized beta; β, standardized beta; BIS, brain injury score; CS, composite score; log, logarithmic scale; SE B, standard error of unstandardized beta; SES, socioeconomic status; SVP, single ventricle physiology; TGA, transposition of great arteries. The reference variable to which the SVP variable and TGA variable were compared was left ventricular outflow tract obstruction. The reference variable to which the centers Utrecht and Zurich were compared was the center London. p-value <0.05*, <0.01**, <0.001***. [a]Benjamini-Hochberg correction for number of tested brain injury scores within primary analysis.

Table III Association of brain injury subscores with cognitive and motor outcome: multiple linear regression models.

Dependent variable	Independent variable	B	SE B	β	t	p	Corrected p[a]	Adjusted R^2
Cognitive CS	Worst hemorrhage score	-0.084	1.423	-0.004	-0.059	0.953	0.953	0.286
	Worst WMI score	-0.495	1.037	-0.033	-0.477	0.634	0.692	0.287
	Worst stroke score	-1.115	1.545	-0.050	-0.721	0.472	0.634	0.288
	Preoperative sum score	-0.756	0.862	-0.063	-0.877	0.382	0.634	0.287
	Postoperative sum score	-0.925	0.809	-0.089	-1.144	0.255	0.634	0.245
Motor CS	Worst hemorrhage score	-1.637	1.352	-0.089	-1.211	0.228	0.634	0.200
	Worst WMI score	-0.856	1.001	-0.063	-0.855	0.394	0.634	0.197
	Worst stroke score	0.899	1.422	0.046	0.632	0.528	0.634	0.195
	Preoperative sum score	-1.333	0.780	-0.128	-1.709	0.090	0.634	0.227
	Postoperative sum score	-0.904	0.753	-0.096	-1.201	0.232	0.634	0.200

Note. B, unstandardized beta; β, standardized beta; CS, composite score; SE B, standard error of unstandardized beta; WMI, white matter injury.

All models were controlled for congenital heart disease subgroup, hospital stay, age at follow-up, and center. Cognitive analyses were additionally

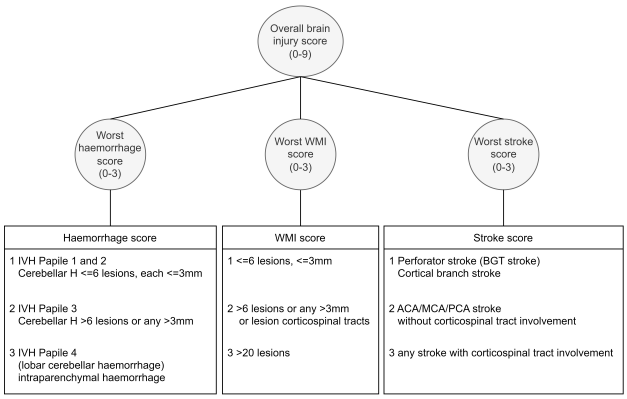
controlled for socioeconomic status. p-value <0.05*, <0.01**, <0.001***. [a]Benjamini-Hochberg correction for number of tested brain injury scores within primary analysis.

Table IV. Association of WMI lesion number and WMI volume/TBV ratio with cognitive and motor outcome: multiple linear regression models.

Dependent variable	Independent variable	B	SE B	β	t	p	Corrected p[a]	Adjusted R^2
Cognitive CS	Preoperative WMI lesions	-0.955	0.448	-0.393	-2.134	**0.042***	0.101	0.132
	Postoperative WMI lesions	-0.551	0.463	-0.181	-1.189	0.242	0.276	0.278
	Preoperative WMI volume/TBV	-44.243	33.802	-0.289	-1.309	0.213	0.276	0.146
	Postoperative WMI volume/TBV	-23.898	54.665	-0.071	-0.437	0.666	0.666	0.252
Motor CS	Preoperative WMI lesions	-1.245	0.356	-0.514	-3.499	**0.002****	**0.012***	0.359
	Postoperative WMI lesions	-1.049	0.444	-0.355	-2.361	**0.023***	0.092	0.194
	Preoperative WMI volume/TBV	-61.667	28.995	-0.377	-2.127	0.050	0.101	0.415
	Postoperative WMI volume/TBV	-96.421	52.342	-0.349	-1.842	0.075	0.120	0.068

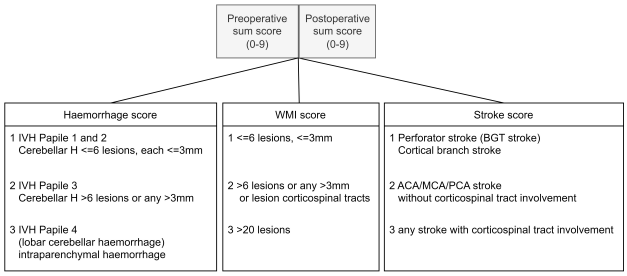
Note. B, unstandardized beta; β, standardized beta; CS, composite score; SE B, standard error of unstandardized beta; TBV, total brain volume, WMI, white matter injury. All models were controlled for congenital heart disease subgroup, hospital stay, age at follow-up, and center. Cognitive analyses were additionally controlled for socioeconomic status. p-value <0.05*, <0.01**. [a]Benjamini-Hochberg correction for number of tested WMI variables.

Figure 1A



Haemorrhage score	WMI score	Stroke score
1 IVH Papile 1 and 2 Cerebellar H <=6 lesions, each <=3mm	1 <=6 lesions, <=3mm	1 Perforator stroke (BGT stroke) Cortical branch stroke
2 IVH Papile 3 Cerebellar H >6 lesions or any >3mm	2 >6 lesions or any >3mm or lesion corticospinal tracts	2 ACA/MCA/PCA stroke without corticospinal tract involvement
3 IVH Papile 4 (lobar cerebellar haemorrhage) intraparenchymal haemorrhage	3 >20 lesions	3 any stroke with corticospinal tract involvement

Figure 1B



Haemorrhage score	WMI score	Stroke score
1 IVH Papile 1 and 2 Cerebellar H <=6 lesions, each <=3mm	1 <=6 lesions, <=3mm	1 Perforator stroke (BGT stroke) Cortical branch stroke
2 IVH Papile 3 Cerebellar H >6 lesions or any >3mm	2 >6 lesions or any >3mm or lesion corticospinal tracts	2 ACA/MCA/PCA stroke without corticospinal tract involvement
3 IVH Papile 4 (lobar cerebellar haemorrhage) intraparenchymal haemorrhage	3 >20 lesions	3 any stroke with corticospinal tract involvement

Figure 4A.
Association of Preoperative WMI Lesion Number with Cognitive Outcome

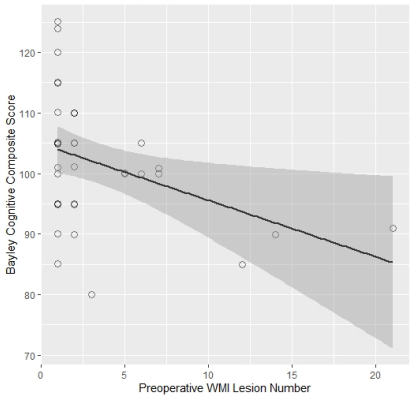


Figure 4B.
Association of Preoperative WMI Lesion Number with Motor Outcome

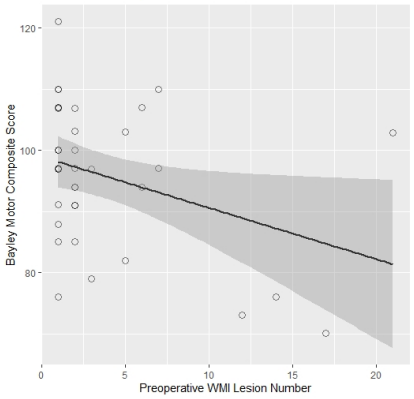


Figure 4C.
Association of Preoperative WMI Volume/TBV Ratio with Motor Outcome