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SYSTEMATIC REVIEW

Early brain magnetic resonance imaging findings and neurodevelopmental outcome in children with congenital heart disease: A systematic review

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Abstract

Aim: To investigate the association between early brain magnetic resonance imaging (MRI) findings and neurodevelopmental outcome (NDO) in children with congenital heart disease (CHD).

Method: A search for studies was conducted in Embase, Medline, Web of Science, Cochrane Central, PsycINFO, and Google Scholar. Observational and interventional studies were included, in which patients with CHD underwent surgery before 2 months of age, a brain MRI scan in the first year of life, and neurodevelopmental assessment beyond the age of 1 year.

Results: Eighteen studies were included. Thirteen found an association between either quantitative or qualitative brain metrics and NDO: 5 out of 7 studies showed decreased brain volume was significantly associated with worse NDO, as did 7 out of 10 studies on brain injury. Scanning protocols and neurodevelopmental tests varied strongly.

Interpretation: Reduced brain volume and brain injury in patients with CHD can be associated with impaired NDO, yet standardized scanning protocols and neurodevelopmental assessment are needed to further unravel trajectories of impaired brain development and its effects on outcome.

As survival of infants with congenital heart disease (CHD) has increased over recent years owing to advances in treatment and care,[1,2] focus has shifted towards improving the long-term outcome of these patients.[3–5] Children with CHD are at risk of neurodevelopmental dysfunction and delay in later life, such as intellectual impairment and poorer executive functioning, which is hypothesized to be caused by prolonged periods of hypoxia and medical interventions inherent to their heart defect.[6] This is reflected in lower IQ scores, decreased cognitive flexibility and inhibition skills, as well as memory, language, and attention deficits.[7–10] Depending on the severity and nature of the impairment, the manifestation of these problems occurs at different ages, ranging from infancy to adulthood.[4,11]

While the causes of the above-mentioned neurocognitive dysfunctions and delays are yet to be discovered, disturbances of brain development, for example brain injury or impaired growth, have been suggested to play a role.[12]

Abbreviations: Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; BSID-II, Bayley Scales of Infant Development, Second Edition; CHD, congenital heart disease; NDO, neurodevelopmental outcome(s); WMI, white matter injury.

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Imaging studies have shown that impairments in the brain are highly prevalent among the population with severe CHD, for example in those with single ventricle physiology or transposition of the great arteries.[13–16] These impairments have been assessed by using qualitative measures of brain injury, such as presence of ischaemic lesions or cerebral haemorrhage,[11,13,16,17] as well as quantitative measures, such as volumetric measurements showing reduced volumes of global or regional brain areas,[11,15] and connectivity analyses, for example demonstrating dysmaturation of the structural connectome in this population.[18]

Although brain injury usually occurs postnatally, altered brain maturation is already seen as early as the second or third trimester of pregnancy.[7,11,15,19,20] Still, the exact role of both reduced brain volumes and brain injury, whether present intrauterine and/or postnatally, in the aetiology of the problems in neurodevelopmental outcome (NDO) of CHD survivors in later life remains unclear.

In recent years, multiple longitudinal cohort studies have attempted to shed light upon this question by investigating quantitative and qualitative measures of the brain as identified on magnetic resonance imaging (MRI) scans and NDO. NDO can be assessed with different global measures, such as IQ or developmental indices, or on specific subdomains of functioning or cognition, for example memory or attention.

The aim of this systematic review is to summarize the findings from studies that investigate the association between qualitative (e.g. brain injury scores) and quantitative (e.g. volumetric measurements or connectivity analyses) measures of the brain as identified by MRI in the first year of life and subsequent NDO in children with severe CHD, who underwent cardiothoracic surgery in the first 2 months of life.

What this paper adds

- Qualitative and quantitative MRI measures in patients with congenital heart defects are associated with neurodevelopmental outcomes.
- Impaired brain development and neurodevelopmental deviations are common problems in patients with congenital heart defects.

METHOD

This systematic review was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions,[21] and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and the AMSTAR-2 checklist.[23] The study protocol and objectives were prospectively registered (PROSPERO CRD42021264047).

Study selection

Studies were eligible for inclusion if they met the following five criteria. (1) Study participants were neonates and/or infants with severe CHD who underwent cardiothoracic surgery in the first 2 months of life. The cut-off was based on clinical experience, as most patients with severe CHD are operated on during this period. Examples of subtypes of severe CHD are transposition of the great arteries, coarctation of the aorta, hypoplastic left heart syndrome, and other univentricular heart defects. (2) Qualitative and/or quantitative MRI of the brain focusing on morphological measures was planned to be performed during pregnancy or in the first year of life. (3) Cognitive and functional neurodevelopment was tested using validated and standardized testing in conjunction with brain MRI, beyond the age of 1 year, and at least 6 months after the first MRI. (4) Associations between findings from brain MRI and NDO were reported. (5) Study type was a randomized controlled trial or observational study (cohort or case–control study). Studies that focused on patient cohorts with syndromal disease or chromosomal defects associated with neurological deficits and those that included infants born very preterm (<32 weeks gestational age) were excluded.

Search strategy

The search strategy was developed in collaboration with a biomedical information specialist of the medical library of the Erasmus MC, using the Population, Intervention, Comparison and Outcome (PICO) format for clinical questions.[24] On 3rd March 2021, a search was conducted in Embase, Medline, Web of Science, Cochrane Central Register of Controlled Trials, PsycINFO, and Google Scholar. A search update was performed on 21st September 2022. The search strategy excluded case reports, conference abstracts published before 2018, and studies not conducted in humans. No language restrictions were applied. For all other article types, all published articles up to the day of the literature search were assessed for eligibility by title and abstract screening. For the search strategy see Appendix S1.

All articles were independently screened on title and abstract by two reviewers (EID and SdM). After consensus was reached, the same reviewers performed the full-text screening. In case of disagreement whether to include a study, consensus was reached in a meeting or a third reviewer (NEMvH) was asked to make the final decision. References of the included articles were independently cross-checked for other relevant studies.

Data extraction

Two reviewers (EID and SdM) independently extracted the data from eligible articles. The following data were extracted: (1) study design and setting; (2) inclusion and exclusion criteria for the patient cohort; (3) presence of a control group, with inclusion criteria if present; (4) population characteristics; (5)

information about the MRI scanner (field strength and scanning sequences used); (6) MRI outcome measures and findings (qualitative and quantitative); (7) neurodevelopmental test(s) performed; (8) neurodevelopmental test(s) outcomes and findings; (9) reported correlations and/or associations between brain imaging and NDO; (10) data on funding of the research.

Data were extracted for all included articles in this review. However, for multiple papers on the same cohort, only the paper describing the largest (part of the) cohort was used to determine the prevalence of specific brain injury subtypes. This also applied to association analyses, meaning that if the same analysis (e.g. between brain volumes and Bayley scores) was done twice in overlapping papers, only the analysis applied to the largest population was used. In cases of different analyses on the same cohort, both papers were included.

Quality appraisal and risk of bias assessment

For quality appraisal, the Critical Appraisal Skills Programme (CASP) checklists for cohort studies and randomized trials were used.[24] For those studies having sufficient quality, levels of evidence were defined by the Centre for Evidence-Based Medicine levels of evidence, on the basis of the study type, study quality, precision, consistency, and effect size. Levels range from 1 to 5, of which level 1 is considered the best.[25]

To assess the internal validity of the included studies, we used the Cochrane Risk of Bias Assessment Tool for Randomized Trials 2,[26] the ROBINS-I for non-randomized studies of interventions,[27] and the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for cohort studies.[28]

Statistical analysis

As acquisition, analysis, and scoring of the imaging data were expected to be very heterogeneous, reflected in different scanning protocols, different reported MRI measures, and differences in neurodevelopmental assessment, pooling of outcomes for meta-analyses was not attempted.

Descriptive statistics, as given in the original articles, are reported as number (percentage), mean (standard deviation [SD]) for normally distributed data, or as median (interquartile range [IQR]) for non-normally distributed data.

RESULTS

The search strategy, including the update, identified 793 unique studies. With title and abstract screening, 740 studies were excluded, leaving 53 for full-text eligibility screening. A total of 18 articles met the inclusion criteria and were included in the review (Figure S1), describing 11 unique cohorts. No additional relevant studies were identified by reference cross-checking. Detailed characteristics of the included studies can be found in Table 1. A list of excluded studies can be found in Table S1, with reasons for exclusion. As all eligible full articles were written in English, no further translation was needed. Quality, as assessed with the CASP checklists, was found to be sufficient in all included studies. Level of evidence was rated as level 3 for 17 studies[18,29–44] and level 4 for one study.[45]

By using the National Institutes of Health Quality Assessment Tool to score risk of bias,[28] of the 17 cohort studies, we rated one as 'good',[38] eight as 'good/fair',[18,29–32,40,43,44] and eight as 'fair'.[33–37,41,42,45] No cohort studies were rated as poor. Therefore, we considered all cohort studies eligible for our review.

As for the randomized controlled trial, rated with Cochrane Risk of Bias Assessment Tool for Randomized Trials 2,[26] it was classified as 'some concerns', because it was unclear whether the person examining neurodevelopment was blinded.[39]

Data on sources of funding per article can be found in Table S2.

Patient selection in included studies

All but one study[42] reported excluding patients with a proven genetic or chromosomal syndrome associated with impaired neurodevelopment. Thirteen studies[18,29–34,37–40,43,44] also excluded patients with a suspicion of a genetic disorder. Fourteen studies excluded infants born preterm; however, different cut-off levels were used: less than 34 weeks gestational age (one study),[34] less than 35 weeks gestational age (two studies from the same cohort),[32,33] less than 36 weeks gestational age (seven studies),[18,29,30,35,38,41,43] less than 37 weeks gestational age (one study),[36] or cut-off was not shown.[40] Median age at surgery was less than 28 days.

Neurodevelopmental outcomes

For an overview of which tests were performed at what ages, see Table 1 and Figure 1.

Three types of neurodevelopmental assessment were used. The first type were assessments that are administered to the child: the Bayley Scales of Infant Development, Second Edition (BSID-II); the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III); the Battelle Developmental Inventory, Second Edition; Wechsler Preschool and Primary Scale of Intelligence, Third Edition; Zurich Neuromotor Assessment; Snijders-Oomen Non-Verbal Intelligence Tests 2–8, Revision; Motor Assessment Battery for Children; and the Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition.[46–52] The second type of assessment was parent-reported outcomes: the Adaptive Behavior Assessment System, Third Edition, was used in one study.[53] The third type were scores for neurological outcome after brain injury: the Paediatric Stroke Outcome Measure[54] and the Glasgow Outcome Scale-Extended.[55] For a more detailed explanation of these tests, see Appendix S2.

TABLE 1 Study characteristics

Reference	Study type	Number included		Types of CHD included	Type of MRI assessment			Timing scan			NDA	Age NDA
					QT			Fetal	Pre-surgery	Post-surgery		
		CHD	Comparison		QL	T1/2	DTI					
Andropoulos et al.[33]	Prospective cohort	30	—	d-TGA	x	—	—	—	Right before	7 days postoperatively	Bayley-III	12 months
Andropoulos et al.[32]	Prospective cohort	59	—	d-TGA, HLHS, SVP, other	x	—	—	—	Right before	7 days postoperatively	Bayley-III	12 months
Beca et al.[41]	Prospective cohort	153	—	TGA, HLHS, SVP, other	x	—	—	—	Not reported	7 days and 3 months postoperatively	Bayley-III	24 months
Wong et al.[45]	Interim analysis	9	51	TGA, HLHS, other	—	x		Not reported	Perioperative		BDI-2	9–36 months
Peyvandi et al.[38]	Prospective cohort	104[a] 70[b]	—	d-TGA, SVP	x	—	x	—	Not reported	Not reported	BSID-II	12 months (1), 30 months (2)
Ramirez et al.[18]	Prospective cohort	14[a] 8[b]	—	TGA, SVP	x[c]	—	x		GA 39.6 (38.7–40.1)	—	Bayley-III	12–18 months, 30 months
Claessens et al.[39]	Data used from RCT	34	—	HLHS, other SVP, other[d]	x	x	—	—	GA 40.6 weeks (SD 1.6)	GA 41.9 weeks (SD 1.7)	Bayley-III, MABC-2, WPPSI-III	24 months (SD 0.7) (1), 6 years (2)
Lim et al.[37]	Prospective cohort	45	—	TGA	x[c]	x	—	—	Age 5 days (1–26)	Age 21 days (4–70)	Bayley-III	18 months
Meuwly et al.[30]	Prospective cohort	50	44	d-TGA, HLHS, other	x	x	—	—	Age 7 days (5–9)	Age 25 days (21–31)	Bayley-III	12 months
Jakab et al.[31]	Prospective cohort	44	—	d-TGA, SVP, other	x[c]	x	—	—	GA 41 weeks (SD 2.2)	GA 43.5 weeks (SD 2.3)	Bayley-III	12 months
Hottinger et al.[29]	Prospective cohort	92	46	d-TGA, SVP, other	x	—	—	—	Age 7 days (5–9)	Age 25 days (20–30)	Bayley-III	13 months (12, 13)
Neukomm et al.[43]	Prospective cohort	57	—	d-TGA, SVP, other	x	x	—		GA 40.5 (1.4), age 7.0 (5.8–9.0)[c]	GA 43.2 (1.8), age 25.0 (20.0–32.0)	WPPSI-III, ZNA, Beery, SON-R	6 years
Kuhn et al.[35]	Retrospective cohort	53	—	d-TGA, HLHS	x	—	—	—	Age 2 days (SD 1.8)	Age 25 days (SD 20)	PSOM, GOS-E	10 months (SD 6)
Kosiorek et al.[36]	Retrospective cohort	42	—	d-TGA, SVP, other	x	—	—	—	Age 4 days (3–5)	Age 33 days (18–50)	PSOM, GOS-E	27.7 months (17–50)
Bonthrone et al.[34]	Prospective cohort	66	219	TGA, HLHS, other	—	x	—	—	GA 39.3 weeks (38.6–39.7)	—	Bayley-III	22 months
Stegeman et al.[40]	Prospective cohort	51		TGA, SVP, other	x	x	x	—	—	Age 15 days (12–21)	Bayley-III	18 months

TABLE 1 (Continued)

Reference	Study type	Number included		Types of CHD included	Type of MRI assessment			Timing scan			Age NDA
		CHD	Comparison		QL	QT T1/2	DTI	Fetal	Pre-surgery	Post-surgery	NDA
Bhattacharjee et al.[42]	Retrospective cohort	17	—	TGA, HLHS, other	x	—	—			Age 160 days (SD 140)	Bayley-III	17–22 months (1), 3 years (2)
Sadwahni et al.[44]	Prospective cohort	52	26	TGA, HLHS, other	—	x	—	GA 28.1 (SD 3.8)			Bayley-III, ABAS-3	22.9 months (SD 4.3)

Values are reported as mean (SD) or median (interquartile range).

Abbreviations: —, not present/performed; ABAS-3, Adaptive Behavior Assessment System, Third Edition; BDI-2, Battelle Developmental Inventory, Second Edition; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; Beery, Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition; BSID-II, Bayley Scales of Infant Development, Second Edition; CHD, congenital heart defect; DTI, diffusion tensor imaging; GA, gestational age; GOS-E, Glasgow Outcome Scale – Extended; HLHS, hypoplastic left heart syndrome; IVS, intact ventricular septum; MABC 2, Movement Assessment Battery for Children, Second Edition; MB-CDIs, MacArthur-Bates Communicative Developmental Inventories; MRI, magnetic resonance imaging; NDA, neurodevelopmental assessment; NR, not reported; PSOM, Pediatric Stroke Outcome Measure; QL, qualitative; QT, quantitative; RCT, randomized controlled trial; SON-R, Snijders-Oomen Non-Verbal Intelligence Tests 2–8, Revision; SVP, single ventricle physiology; (d-)TGA, (dextro-)transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition; ZNA, Zurich Neuromotor Assessment.

[a]Follow-up at 12 months.

[b]Follow-up at 30 months.

[c]Data not used in association analysis.

[d]Inclusion criterion: need for aortic arch reconstruction with cardiopulmonary bypass.

An overview of all NDO, including timing of tests when NDO was measured at multiple time points, is given in Table S3.

Three studies compared neurodevelopmental scores of infants with CHD with controls[29,30,44] and found significantly lower mean cognitive and motor composite scores in infants with CHD. Additionally, a lower mean language composite score among infants with CHD compared with typically developing individuals was found in one study.[44]

Qualitative MRI findings

For a detailed overview of qualitative measures, including pre- and postoperative prevalence of brain injury, see Table S4.

Fifteen studies reported findings from qualitative evaluation of the brain MRI scans.[18,29–33,35–43] Sixteen studies assessed prevalence of ischaemic stroke and/or infarction.[18,29–41,44,45] Other qualitative measures included focal or multifocal white matter injury (WMI),[18,29,30,32,33,35–45] and brain haemorrhage, including intraparenchymal, intraventricular as well as subdural haemorrhage.[31–33,35–37,41] Moreover, five studies used a composite brain injury score, such as the Total Maturation Score[56] by Childs et al.,[29,32,36,41] the Brain Injury Severity score,[38,43] the brain injury scoring system by Andropoulos et al.,[35,36,57] and the adapted scoring system used by Bhattacharjee et al.[42]

Preoperative prevalence of brain injury of any type ranged from 23% to 61%,[30,32,35,37–39,41] with WMI being the most prevalent subtype (20–61%).[30,32,35,37-39,41] The prevalence of infarction/ischaemia ranged from 5% to 26%,[30,32,35,37,38,41] and that of brain haemorrhage from 2% to more than 13%.[31,32,35,37,41]

Postoperative prevalence of brain injury of any type ranged from 20% to 79%,[29,32,35,37,39–41] again with WMI as the most commonly found subtype (20–79%).[35,37,39–41] Infarction or ischaemic stroke was found in 7% to 20%,[31,35,37,40] and brain haemorrhage in 2% to 22%.[31,35,37]

New postoperative brain injury was found in all studies that specifically addressed this.[30,32,35,39,41] This new injury included WMI,[30,32,35,39,41] infarction/ischaemic stroke,[32,35,41] and brain haemorrhage.[32,35,41] No signs of new injury were found on late postoperative scans compared with early postoperative ones.[41]

Associations between qualitative MRI findings and NDO

A full overview of the associations between qualitative MRI findings and NDO can be found in Table 2, Table S5, and Figure 1.

Seven[29,32,33,36,38,39,41] out of 11 studies investigating associations between qualitative findings and NDO reported one or more significant associations or correlations between NDO and qualitative MRI findings.

New postoperative brain injury,[32] neonatal WMI,[39] and lower brain maturity score on 3-month MRI[41] correlated

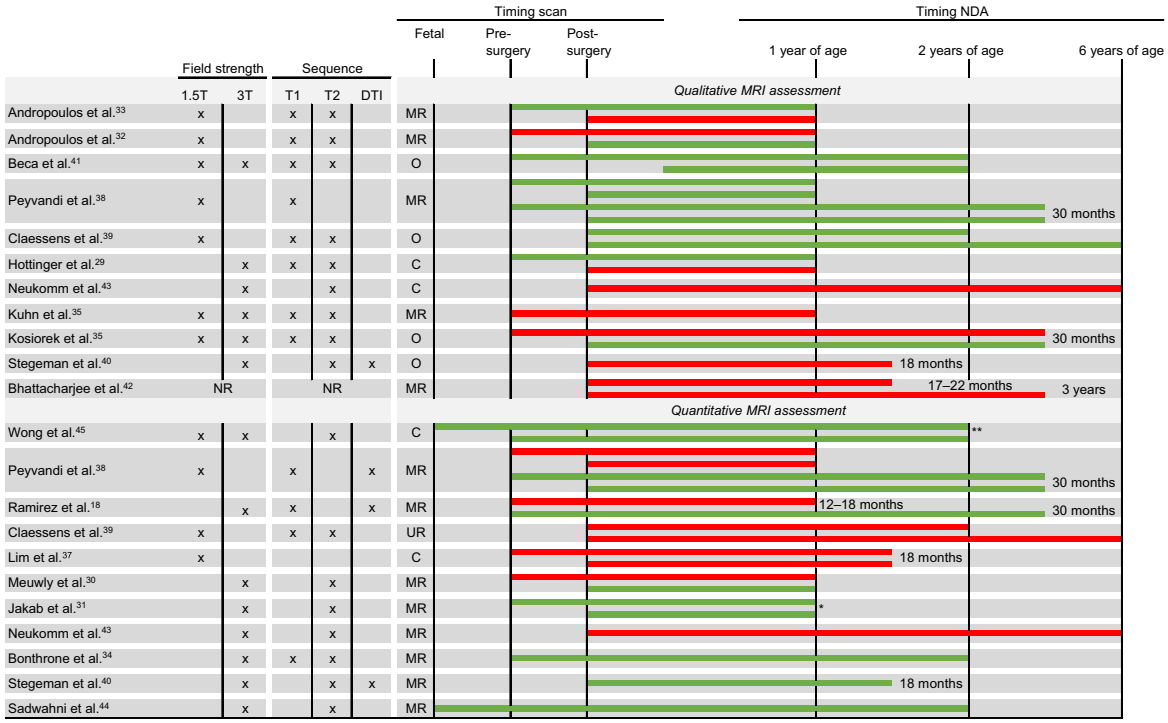

FIGURE 1 Associations and correlations between MRI assessment and neurodevelopmental outcome. *Growth measurement covering pre- and postoperative scans. **Brain growth covering three time points; neurodevelopment assessed between 9 and 36 months. Green bars, association between MRI assessment and neurodevelopmental outcome; red bars, no association between MRI assessment and neurodevelopmental outcome. Abbreviations: C, correlation; DTI, diffusion tensor imaging; MR, multivariable regression; MRI, magnetic resonance imaging; NDA, neurodevelopmental assessment; NR, not reported; O, other statistical analysis; T, tesla; UR, univariable regression.

negatively with the cognitive composite score. New postoperative brain injury,[32] lower brain maturity score on 3-month MRI,[41] as well as preoperative brain injury[33] were associated with lower language composite score, whereas higher brain injury severity score[38] was associated with lower Psychomotor Development Index (PDI) scores. Moreover, brain maturity scores on 3-month MRI[41] and preoperative brain injury[33] were associated with lower motor composite score. Another study reported a higher odds of motor problems among those with injury of the posterior limb of the internal capsule.[39] This study also found neonatal WMI to be associated with lower Full-Scale IQ and higher teacher report of attention problems at 6 years. Moreover, presence of postoperative infarction and/or intraparenchymal haemorrhage associated with increased risk of adverse outcome as assessed by the Paediatric Stroke Outcome Measure.[36] At 9 months of age, infants with neonatal WMI showed significantly lower gross motor scored than those without it.[40]

Quantitative MRI findings

Eleven studies used some form of quantitative assessment of the brain,[18,30,31,34,37–40,43–45] for example brain volume,[30,34,39,40,43,44] brain volume growth rate (millilitres/year during scan interval),[31] fractional anisotropy,[18,38,40] mean diffusivity,[40] structural connectivity (i.e. graph theory, on the basis of measures of fractional anisotropy),[18] brain weight based on brain volumes and autopsy data,[37] and cross-linear measurements in the axial plane (millimetres).[45]

Two of the six studies measuring brain volumes found significantly smaller total brain volumes compared with either typically developing comparison individuals or normative means.[30,34] Smaller regional volumes were also found, including significantly smaller frontal lobe[30,34] and cerebral grey matter[58] Significantly smaller regional volumes were demonstrated for basal ganglia, thalamus, and brainstem in children with a below-average IQ compared with those having an average and above-average IQ.[39]

Internal closure of bilateral opercula was found to be delayed compared with typically developing individuals, and cerebellar sagittal vermis height was significantly smaller in the group with CHD.[45] Studies that reported on brain volume growth and brain weight,[31,37] and on fractional anisotropy,[38,40] did not compare infants with CHD and typically developing individuals.

Associations between quantitative MRI findings and NDO

A full overview of the associations between quantitative MRI findings and NDO can be found in Table 3, Table S6, and Figure 1.

Four out of six studies on brain volume found significant associations between brain volumes and NDO.[34,39,40,44]

TABLE 2 Qualitative MRI measures: statistically significant results in relation to neurodevelopmental outcome

Reference	Qualitative outcome measures	Neurocognitive measure	Statistical analysis	Significant results	*p*	Covariates
Andropoulos et al.[33]	Preoperative brain injury	LS, MS	Multivariable linear regression	β LS: −27.38 (−40.14 to −14.63) β MS: −25.01 (−34.15 to −15.87)	<0.001 <0.001	Intraoperative rSO2, ICU LOS, midazolam first 12 months, chromosome anomaly, MIQ
Andropoulos et al.[32]	New postoperative brain injury	CS, LS	Multivariable linear regression	β CS: −6.85 (−13.36 to −0.34) β LS: −6.96 (−12.79 to −1.13)	0.039 0.020	Preoperative MRI injury, MAC-hour VAA, fentanyl equivalents, benzodiazepine equivalents, preoperative mean rSO2 (CS, MS), ICU LOS, aprotonin (LS, MS), abnormal chromosomes (MS, LS)
Beca et al.[41]	Maturation posterior limb of internal capsule	MS	One-way ANOVA	—	0.049	
	Brain maturity score on 3-month MRI	MS, LS, CS	Linear regression	r MS: 0.36 r LS: 0.21 r CS: 0.25	<0.001 0.024 0.007	
Peyvandi et al.[38]	BIS (BIS = 2 vs BIS = 0)	PDI	Stratified multivariable linear regression	β d-TGA: −14.2 (−27.1 to −1.2) β SVP: −13.8 (−27.8 to 0.1)	0.03 0.05	Site, MEL, BAS
Claessens et al.[39]	Neonatal WMI (moderate–severe vs no-mild)	CS at 2 years, Full-Scale IQ, and teacher report of attention problems at 6 years	Corrected difference	CS: −11 (−22 to −1) Full-Scale IQ: −14 (−29 to 0) Attention problems: 6 (0–12)	<0.05 <0.05 <0.05	
	PLIC injury	Motor problems	Odds ratio	12.1 (1.2–123.6)	<0.05	
Hottinger et al.[29]	No associations found between brain maturation scores and neurodevelopmental outcome					
Neukomm et al.[43]	No associations found between cumulative brain injury score and neurodevelopmental outcome					
Kuhn et al.[35]	No associations found between brain injury scores and neurodevelopmental outcome in multivariable linear regression					Diagnosis (HLHS vs d-TGA), ICU LOS > 24 days, DHCA >40 minutes, total duration of ventilation >12 days, preoperative total brain injury score ≥6
Kosiorek et al.[36]	Postoperative infarction and/or intraparenchymal haemorrhage	PSOM	Prevalence difference between good and poor outcome	13% vs 67%	0.018	
			Univariable logistic regression poor PSOM outcome	Not reported	0.018	Not reported

(Continues)

TABLE 2 (Continued)

Reference	Qualitative outcome measures	Neurocognitive measure	Statistical analysis	Significant results	*p*	Covariates
Stegeman et al.[40]	No differences in neurodevelopmental outcome found between individuals with and without neonatal WMI or arterial ischaemic stroke and neurodevelopmental outcome					
Bhattacharjee et al.[42]	No associations found between brain abnormality scores and neurodevelopmental outcome in multivariable linear regression					GA, birthweight, sex, Apgar score, age at NDA, SaO2 before surgery, hematocrit level after surgery, respiratory index before and after surgery, aortic cross-clamping time, lactate level, and age at MRI

Significant results are reported as estimate (95% confidence interval) when provided.

Abbreviations: ANOVA, analysis of variance; BAS, balloon atrial septostomy; BIS, brain injury severity; CI, confidence interval; CS, cognitive composite score; DHCA, deep hypothermic circulatory arrest; GA, gestational age; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; LOS, length of stay; LS, language composite score; MAC, minimum alveolar concentration; MEL, maternal education level; MRI, magnetic resonance imaging; MS, motor composite score; NDA, neurodevelopmental assessment; PDI, Psychomotor Development Index; PLIC, posterior limb of the internal capsule; PSOM, Paediatric Stroke Outcome Measure; rSO2, regional cerebral oxygen saturation; SaO2, systemic oxygen saturation; SVP, single ventricle physiology; (d-)TGA, (dextro-)transposition of the great arteries; VAA, volatile anesthetic agents; WMI, white matter injury.

Atypicality indices, which represent the degree of deviation of a regional volume from the normative mean, in the bilateral thalamus and caudate and left lentiform nucleus were positively correlated with cognitive composite scores[34] in the complete sample, which included children born before 37 weeks gestational age. Analysis of a subsample of children born after 37 weeks gestational age showed grey matter and total tissue atypicality indices to be significantly associated with cognitive outcome.[34] Children with a below-average IQ (<85) showed smaller neonatal brain volumes and decreased cortical measures postoperatively, at a mean postmenstrual age of 41 weeks, compared with children with an average or above-average IQ (≥85), which was significant for basal ganglia, thalamus, and brainstem.[39] At 18 months of age, smaller cerebellar volume was associated with lower fine motor scores.[40] As for the five studies that used quantitative measurements other than volume as such, three found a correlation with outcome.[18,31,45] Brain volume growth between the pre- and postoperative scan of the left posterior perisylvian region was significantly positively correlated with language score.[31] Cerebellar inferior vermis width, measured postoperatively, was associated with lower scores in the communication, cognitive, personal–social, and total developmental quotients. Furthermore, reductions in scores of the adaptive developmental quotient correlated with smaller cross-linear measurements of the left cerebellar hemisphere, as manually assessed.[45] Regarding structural connectivity, global efficiency (a measure of network integration, the inverse of the mean shortest path between any two regions of interest) was significantly positively associated with motor scores at 30 months of age.[18] Neither brain weight z-score nor white matter fractional anisotropy values were associated with neurodevelopmental measures.[37,38]

Timing

MRI was performed at different time points in the different studies. For an overview of timing of MRI scans and neurodevelopmental assessment, see Table 1 and Figure 1. Regarding moment of scanning, 8 out of 14 studies found an association between either quantitative or qualitative findings on MRI made preoperatively and NDO,[18,29,31,33,34,38,41,45] and 7 out of 14 found associations based on MRI scans made postoperatively.[30–32,36,38,40,45] The exact age of the patients at which the scan and/or surgery took place was not reported in all papers; therefore, this remains unclear for some studies.

DISCUSSION

In this review, we integrated the literature on the association between findings on brain MRI in the first year of life and NDO later in life in children with CHD, with age at follow-up ranging from 1 to 6 years. Both brain injury and deviant quantitative brain metrics are common in this population of patients. Given the heterogeneity between studies, mainly

TABLE 3 Quantitative MRI measures: statistically significant results in relation to neurodevelopmental outcome

Reference	Quantitative MRI measure	Neurocognitive measure	Statistical analysis	Significant results	*p*	Covariates
Wong et al.[45]	Cerebellar inferior vermis width (postoperative)	Expressive communication, personal–social DQ, communication DQ, cognitive DQ, total DQ	Spearman's rho rank correlation	Expressive communication $\rho -0.92$, personal–social DQ −0.93, communication DQ $\rho -0.92$, cognitive DQ $\rho -0.95$, total DQ $\rho -0.91$	<0.017	—
	Right cerebellar hemisphere (preoperative)	Fine motor		Fine motor ρ 0.95		
	Brain biparietal diameter (preoperative)	Self-care, adaptive DQ		Self-care $\rho -0.86$, adaptive DQ $\rho -0.86$		
Peyvandi et al.[38]	WMI volume	PDI	Multivariable linear regression	β PDI: − 0.06 (−0.110 to − 0.009)	0.02	Site, cardiac group, maternal education, balloon atrial septostomy
Ramirez et al.[18]	Global efficiency[a]	MCS	Multivariable linear regression	β MCS: 43 (6.5–80.8)	0.02	Cohort (ref: HIE), sex, GA at MRI
Claessens et al.[39]	No associations found between brain volumes or cortical measures and neurodevelopmental outcome					—
Lim et al.[37]	No correlation found between brain weight z-score and neurodevelopmental outcome					
Meuwly et al.[30]	Postoperative frontal volume	CCS, LCS	Multivariable linear regression	β CCS: 0.02 (0.00–0.04), β LCS: 0.021 (0.00–0.004)	0.043, 0.04	Sex, PMA at MRI, MRI cohort, SES, ICU LOS
	Postoperative temporal volume	CCS, LCS		β CCS: 0.039 (0.01–0.07), β LCS: 0.032 (0.00–0.06)	0.014, 0.046	
	Postoperative cerebellar volume	CCS		β CCS: 0.056 (0.01–0.1)	0.018	
	Postoperative cortical volume	LCS		β LCS: 0.0079 (0.00–0.02)	0.045	
Jakab et al.[31]	Brain growth rate of the left posterior perisylvian region	LCS	Multivariable linear regression	β LCS: 0.025 (0.015–0.035)	<0.001	Hospital LOS
Neukomm et al.[43]	No associations found between postoperative total brain volume and neurodevelopmental outcome in multivariable linear regression					Postoperative TBV, cumulative BIS score, CHD complexity, length of hospital stay, SES
Bonthrone et al.[34]	Left thalamus AI	CCS	Multivariable linear regression	β 0.41	0.006	Index of multiple deprivation
	Right thalamus AI	CCS		β 0.39	0.011	
	Left caudate nucleus AI	CCS		β 0.33	0.017	
	Right caudate nucleus AI	CCS		β 0.35	0.016	
	Left lentiform nucleus AI	CCS		β 0.30	0.043	
Stegeman et al.[40]	Cerebellar volume	Scaled fine motor score 18 months	Multivariable linear regression	β 2.80 (0.47–5.12)	<0.05	PMA at time of MRI, repeated cardiac surgery

(Continues)

TABLE 3 (Continued)

Reference	Quantitative MRI measure	Neurocognitive measure	Statistical analysis	Significant results	*p*	Covariates
Sadhwani et al.[44]	Total fetal brain volume	CCS	Multivariable linear regression	*β* 0.28 (0.08–0.48)	<0.05	White ethnicity, stroke/seizure, LOS
		LCS		*β* 0.32 (0.03–0.60)		Education level
		MCS		*β* 0.32 (0.09–0.55)		Sex, cardiac class, LOS, ECMO
		Expressive communication		*β* 0.06 (0.014–0.12)		Education, ECMO
		Fine motor		*β* 0.05 (0.003–0.10)		Sex, LOS
		Gross motor		*β* 0.06 (0.02–0.10)		Ethnicity, cardiac class, ECMO
		ABAS-3 general adaptive composite		*β* 0.49 (0.22–0.76)		—

Significant results are reported as estimate (95% confidence interval) when provided.

Abbreviations: ABAS-3, Adaptive Behavior Assessment System, Third Edition; AI, atypicality index; BIS, brain injury severity; CCS, cognitive composite score; DQ, developmental quotient; ECMO, extracorporeal membrane oxygenation; GA, gestational age; HIE, hypoxic–ischemic encephalopathy; ICU, intensive care unit; LCS, language composite score; LOS, length of stay; MCS, motor composite score; MDI, mental developmental index; MRI, magnetic resonance imaging; PDI, psychomotor developmental index; PMA, postmenstrual age; SES, socioeconomic status; TBV, total brain volume.

[a]Log of global efficiency.

because of the different para-meters assessed and estimated, not one convincing association between type of brain metric and NDO stands out. Therefore, the predictive value of a specific qualitative measure or the volume of a specific brain region remains unsure. However, most studies found evidence for more severe brain injury or smaller brain volumes being correlated with worse NDO.

Studies on either brain MRI findings or NDO have been reviewed before,[8,15,59] showing that both brain lesions and neurodevelopmental delay are common in this population of patients. Reviews by Mebius et al.[15] and Khalil et al.[60] considered both brain imaging findings and NDO and both found indications for brain injury and deviant brain development to be associated with impaired NDO. Mebius et al.[15] included only a few studies concerning this association, as not many were available at that time. Yet, their conclusions agree with our findings. Khalil et al.[60] focused mainly on neurological examination in the first weeks of life, which is different from the approach we took. Moreover, both studies included not only brain MRI but also ultrasound imaging, which is considered less suitable for assessing brain injury or brain development, given the high risk of false-positive findings and the fact that MRI provides more accurate and more detailed information.[61–63]

We evaluated both qualitative and quantitative measures of the brain in relation to NDO. Both methods showed abnormalities in a considerable number of infants. With qualitative evaluation, lesions pertained mostly to WMI and ischaemic stroke/infarction and were found in 23% to 61% of the neonates and infants preoperatively.[30,32,35,37,39–41] Postoperatively this percentage was higher in most studies and ranged from 20% to 79%,[29,32,35,37,39–41] indicating that many infants developed new brain injury perioperatively. Previous MRI studies that focused solely on qualitative brain injury, without taking subsequent NDO into account,[6,13,64–67] have found percentages of brain injury that are in line with the findings in our review.

As for quantitative brain assessment, two out of six studies that studied brain volumes found a reduction in total brain volume as well as in specific regions of interest in infants with CHD compared with typically developing infants,[30,34] which is in line with recent literature focusing solely on brain volumes in patients with CHD.[68–70]

With respect to NDO, three studies included in this review that compared results between CHD survivors and typically developing individuals found significantly lower cognitive and motor scores for CHD survivors[29,30,44] (Table S3), as well as lower language scores.[44] This trend on neurodevelopment is in line with other studies that solely studied neurodevelopment in this population;[71,72] therefore, we consider our results as representative for the CHD population.

Of the studies included in this review, 7 out of 18 assessed both quantitative and qualitative measures of the brain.[30,31,37-40,43] However, only 3 out of 16 investigated the association of qualitative and quantitative measures of the brain with NDO in the same cohort.[38,39,43] None of these

three studies investigated whether the associations between NDO and qualitative or quantitative assessments respectively, were correlated, although Peyvandi et al.[38] stated that the association between quantitatively measured WMI volumes and PDI scores at 2 years of age was in line with their qualitative findings related to PDI at the same age.

Even though we found associations between MRI findings and NDO, results related to timing were not consistent. Eight out of 14 studies found an association between qualitative and/or quantitative findings on preoperative MRI scans and NDO,[18,29,31,33,34,38,41,45] and 7 out of 14 studies found associations based on postoperative MRI scans[30–32,36,38,40,45] (Figure 1). Explanations for the inconsistency present in these findings can be found at the level of both brain assessments and neurodevelopmental tests.

Given the heterogeneity in findings about the association between brain MRI and NDO, the impact of potential risk of bias of the individual studies is difficult to determine. The only randomized controlled trial that was included scored highly on risk of bias and did find an association between neonatal WMI and NDO measures,[39] whereas all other studies investigating WMI and NDO did not. If the assessors of NDO in this study were indeed not blinded, their knowledge of the brain injury history of patients could have led to differential assessment of NDO for those with and without signs of brain injury on neonatal MRI scans. However, this study did not find an association between quantitative measures and NDO, which is not what might be expected in the case of NDO assessment not blinded to MRI findings. As we did not rate any of the included non-randomized studies as 'poor' in the risk of bias assessment, any likely impact of risk of bias is minimal. Most of the included non-randomized studies found associations between both qualitative as well as quantitative MRI measures and NDO; no obvious effect of potential risk of bias in the non-randomized studies on our results was observed.

Regarding MRI, the timing of the MRI scans varied among studies, complicating comparison of the findings. Traditionally, origin of brain injury in infants and children with CHD was hypothesized to rely mostly on cardiac surgery and subsequent events,[73–77] which argues for scanning after surgery. However, in recent years evidence has emerged that delay or deviation in brain development already starts during pregnancy, thus before any medical procedure has taken place.[7,15,19,64,74,77,78] Early alterations in, for example, cerebral blood flow cannot only directly lead to brain injury and delayed brain development, but also predispose children with CHD to further brain injury in later life.[7,64] By demonstrating that not only postoperative but also preoperative brain deviations (assessed either qualitatively or quantitatively) associate with NDO, our review emphasizes the importance of scanning as early in life as possible[18,29,31,33,34,38,41,45] (Figure 1). Yet, to predict NDO later in life most reliably, the optimal time point to scan the brain remains unknown. Thus far, fetal, preoperative, and postoperative scans show brain injury and deviant brain development over time in the first year, without clear evidence that injury or impairment at a specific time point is more predictive for later NDO than at other time points. Moreover, brain injury seems to accumulate over time, because the brain of children with CHD is especially vulnerable to cerebral blood flow alteration caused by the CHD and subsequent treatment.[71,79] Intuitively, one could argue for not performing brain imaging too early. However, given the increasing evidence for early brain injury and early deviant brain development being a substrate for more injury or more severe developmental delay[7,64] due to, for example, cardiac surgery, the identification of already-deviant fetal brain development in CHD may be important for the development of interventions to support the brain's plasticity in utero.

Furthermore, the type and consequently the severity of CHD might affect brain development and neurodevelopment. The hypothesis is that more severe types of CHD are associated with more complex or extensive brain injury and worse NDO. For example, Claessens et al. found a relatively high prevalence of WMI in a study population that consisted of children with aortic arch obstruction,[39] whereas single ventricle pathology and transposition of the great arteries are known for their altered neurovascular physiology affecting brain development in utero.[64] By including only studies on severe CHD in this review, we aimed to select a specific group of patients. Yet, the heterogeneity of CHD types between and within studies included in this review prevent us from drawing conclusions on this topic, but variety in severity and pathophysiology of CHD should be considered while interpreting results of both brain imaging as well as NDO studies in patients with CHD. If this were true, the type of CHD could help in deciding which patients with CHD need to be monitored more closely for brain development and NDO.

Considering postnatal brain injury, surgical factors are said to be easiest to treat,[77] which emphasizes the importance of evaluating the effect of cardiac surgery on brain injury and brain development by comparing pre- and postoperative brain imaging and quantifying the consequences of surgery-related factors on the brain. However, the association between specific surgical factors, such as the use of deep hypothermic arrest or (duration of) cardiopulmonary bypass, and brain injury[16,41,65] or NDO[41,72,77,80–82] is not consistently reported. Likewise, factors related to the severity of illness, such as extra-corporeal membrane oxygenation treatment, length of stay on the (paediatric) intensive care unit, and administration of certain drugs (e.g. inotropes) and nutrition (e.g. glucose and parenteral nutrition), have been suggested to contribute to the multifactorial causes of brain injury and deviant neurodevelopment, and should therefore not be neglected.[3,83–88] Often, information on factors related to socioeconomic status was lacking, while in previous research the association between socioeconomic status and outcome has been demonstrated both in typically developing children and in children with CHD.[89,90] Yet, as approaches towards statistical correction for covariates, for example socioeconomic status, varied strongly, no conclusions could be drawn.

Standardized reporting and categorization of such clinical parameters in future studies will help to better unravel the specific sequelae preceding brain injury and deviant neurodevelopment in this population of vulnerable patients. In addition, these at-risk children would ideally undergo a series of brain MRI scans at several time points before, during, and after treatment. These scans should extend at least until after myelination and completion of the structural maturation of the brain, and preferably start in utero, to longitudinally monitor brain development and subsequent NDO. Population-based studies focusing on brain development in typically developing children form a reference group that can be used to compare the brain development of patients with CHD. Eventually, this will help to understand the origin of disturbances of brain development, on which intervention strategies can be based.

Another comment about MRI findings is that we were unable to study the localization of the reported lesions related to outcome, as results varied strongly. Yet, location is of importance in future studies, because some regions might be more vulnerable than others, which is manifested in certain neurodevelopmental domains.[91] This has, for instance, been demonstrated for the hippocampus, with respect to memory functioning.[92]

Standardized scanning protocols will provide insight into localization, severity, and timing of onset of injuries, even more so when scored according to a harmonized protocol. This has recently been done across several European centres and, with a standardized scanning protocol, is of use when aiming for consensus in brain MRI findings.[93] Similarly, standardized software is needed to assess quantitative measurements as brain volume, to gain structured insight in brain growth, globally as well as regionally.

Concerning the NDO findings, some remarks must be made. First, most of the included studies applied the Bayley-III to assess NDO. However, it has recently been demonstrated that survivors of CHD assessed with the Bayley-III have better outcome scores than patients assessed with the BSID-II.[94–96] A potential explanation is that children with mild impairment were included in the standardization sample of the Bayley-III, which was not the case for the BSID-II.[97] Moreover, the total BSID-II score is dependent on language scores, whereas those were removed for the Bayley-III to test (non-verbal) cognition more clearly, yet this simplifies the Bayley-III compared with BSID-II. This has implications for interpreting associations between brain MRI and outcome. That is, had the BSID-II been used instead of the Bayley-III, stronger associations might have been found.

Second, neurodevelopment was assessed between 1 and 6 years of age, of which many (i.e. in 8 out of 18 studies[18,29–33,35,38]) were at 1 year of age (Figure 1). This is of concern when drawing any conclusions, because it has been demonstrated that neurodevelopment at 1 year of age is not yet predictive of NDO later in life.[98] Some neurodevelopmental problems might only become evident at school age, a phenomenon that is often referred to as a growing-into-deficit. Brain injury acquired in early life only functionally becomes known once higher neurocognitive functioning is demanded at a later age. This is emphasized by studies demonstrating that around school age and beyond, survivors of CHD are at risk of several neurocognitive delays, with impaired (visual–spatial) memory being one of the most common, which could not have been assessed earlier in life.[99–101]

As for assessment of NDO, a standardized test battery with a minimum of neurodevelopmental tests that can be assessed in all children in this patient group, preferably at least up until school age, is needed. Recently, the Cardiac Neurodevelopmental Outcome Collaborative has proposed such batteries, both for preschool and school-aged children, which should be considered for future studies.[102,103] As adequate neurodevelopmental testing can only be performed at older ages, longitudinal studies with longer follow-up duration are needed. Other, more objective methods such as eye-tracking to study neurodevelopment may be of use as well.[104] Parent-reported executive functioning can also be useful as an addition to objective tests. Objective tests are not often used in a clinical setting at a young age, because the concepts involved are too difficult to assess or because standardized tests are not available owing to the age limitations of the tests. Yet, even in older children it is desirable to obtain both objective and subjective (i.e. parent-reported) measures, as these complement each other. It must be taken into account that parents tend to perceive their child's problems as being more severe, compared with self-reported outcomes.[10,105] Moreover, adding emotional and behavioural measures to the test battery could be of interest, given the relatively high prevalence of behavioural dysregulation in patients with CHD later in life.[106,107] Ideally, findings about both brain measures, as well as NDO and their association, would be investigated for certain categories of heart defects separately (e.g. transposition of the great arteries and single ventricle physiology), acknowledging the differences in circulatory aspects and their potential effect on brain development and NDO.

This review included a relatively small number of studies, further reduced by the overlap in samples between the studies. Also, two of the included studies had very limited sample sizes ($n < 15$) and their reported results should therefore be interpreted with caution.[18,45] Twelve of the 18 included studies were published in the 4 years before 2023,[18,29–31,34–37,40,42–44] highlighting the increased attention given to this field of research. By reviewing all available literature up to now, it has become clear that research into brain imaging and (subsequent) NDO in the population with CHD is necessary, given the high prevalence of brain injury, deviant brain development, and impaired NDO. However, to draw definitive conclusions on associations between either specific qualitative or quantitative MRI measures and outcome, variations in approaches towards MRI and NDO assessment must be reduced.

Another limitation of this research field is related to patient selection and reporting on clinically relevant information, resulting in non-uniformity between cohorts. For

example, studies used different criteria for preterm birth. Also, the extent of exclusion of all individuals with genetic syndromes could often not be verified as information on standard practice of genetic testing was not reported. Therefore, direct comparison and pooling of the results found in the different cohorts would lead to results that could not be interpreted reliably. Lastly, publication bias is difficult to rule out in this type of study, as those showing significant associations between MRI and outcome might have had higher chances of publication.

CONCLUSION

Early brain injury, impaired brain development, and neurodevelopmental delay are common problems in children with CHD. Impaired brain development and brain injury in patients with CHD are associated with impaired NDO, yet an exact association between specific brain MRI findings and specific later NDO remains unclear, because findings of different studies vary strongly. To optimize the comparability of studies and the possibility of adequately studying the association between these variables, standardization and harmonization of brain MRI and neurodevelopmental assessments is crucial.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1. Search strategy.
Appendix S2. Explanation of neurodevelopmental tests analysed.
Figure S1. Flowchart showing the search of eligible studies for inclusion.
Table S1. List of excluded studies based on full-text screening.
Table S2. Sources of funding of the included studies.
Table S3. Neurodevelopmental outcomes.
Table S4. Pre- and postoperative prevalence of qualitative MRI measures.
Table S5. Qualitative MRI measures and neurodevelopmental outcome.
Table S6. Quantitative MRI measures and neurodevelopmental outcome.

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