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# Neurodevelopmental delay with critical congenital heart disease is mainly from prenatal injury not infant cardiac surgery: current evidence based on a meta-analysis of functional magnetic resonance imaging

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**KEYWORDS:** cardiac surgery; congenital; heart defects; magnetic resonance imaging; meta-analysis; neurological development

## ABSTRACT

***Objective*** *No consensus has been reached regarding whether brain injury related to congenital heart disease (CHD) is caused by infant cardiac surgery and/or prenatal injury resulting from the CHD. We performed this meta-analysis to identify the likely cause of neurodevelopmental delay in CHD patients.*

***Methods*** *We carried out a literature search without language restriction in December 2013, retrieving records from PubMed, EMBASE, the Cochrane Library and the World Health Organization trials center, to identify studies applying functional magnetic resonance imaging (fMRI) evaluation of brain function before surgery and, in some cases, after surgery (both immediate term and short term postoperatively). The preoperative and postoperative fMRI results were extracted, and meta-analysis was performed using Revman 5.1.1 and STATA 11.0, according to the guidelines from the Cochrane review and MOOSE groups.*

***Results*** *The electronic search yielded 937 citations. Full text was retrieved for 15 articles and eight articles (nine studies) were eligible for inclusion: six studies (*n = *312 cases) with fMRI analysis before surgery and three (*n = *36 cases) with complete perioperative fMRI analysis. The overall average diffusivity of CHD cases was significantly higher than that of controls, with a summarized standard (std) mean difference of 1.39 (95% CI, 0.70–2.08), and the fractional anisotropy was lower in CHD cases, with a summarized mean difference of −1.43 (95% CI, −1.95 to −0.91). N-acetylaspartate (NAA)/choline (Cho) for the whole brain was significantly lower in CHD cases compared with healthy ones, while lactate/Cho was significantly higher in CHD cases. Immediate term postoperatively, significant changes in NAA/creatine and NAA/Cho, relative to preoperative values, were found. However, the difference did not persist at the short-term follow-up.*

***Conclusion*** *This meta-analysis suggests that the delay in neurological development in newborns with CHD is due mainly to prenatal injury, and cardiac surgery might lead to mild brain injuries postoperatively, but fMRI shows recovery within a short period.* Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

## INTRODUCTION

Congenital heart disease (CHD) is one of the most common congenital abnormalities[1]. Surgical repair during the neonatal or infant period is essential for survival of some critical cases[2]. Though neurobehavioral and neurological disorders are common in children with critical CHD, it remains unclear whether early surgical intervention, critical CHD itself, or both, has a negative impact upon the patients' neurological performance. Previous studies using magnetic resonance imaging (MRI) have found postoperative periventricular leukomalacia and white-matter injury after cardiopulmonary bypass[3]. A previous meta-analysis suggested delayed motor and cognitive development, and even intellectual and neuromotor

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impairment in adolescence, after early surgery for CHD, but failed to perform dedicated assessment of neurological performance both preoperatively and postoperatively[4]. As a result, the exact time of onset regarding neurodevelopmental delay could not be confirmed.

In recent years, functional MRI (fMRI) has been applied in the quantitative measurement of brain development[5], allowing early assessment and frequent monitoring. The correlation between fMRI evaluation and other neurodevelopmental assessment tools has confirmed its value in evaluating brain function[6–8]. Among the specific fMRI protocols, diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) have been used widely to measure the brain microstructure and metabolic profile of neonates and infants[9,10]. The 'average diffusivity' (Dav) from DTI characterizes the pattern of water diffusion as evidence of microstructural development: decreased Dav is observed as a result of water reduction in tissue, which suggests development of neuronal cells and therefore brain maturation. Conversely, if MRS measurement shows induction of N-acetylaspartate (NAA), reduction of lactate (Lac) or induction of creatine (Cr), brain impairment is indicated.

Although localized lesions associated with cardiopulmonary bypass (e.g. periventricular leukomalacia, white-matter injury) can be identified by routine MRI, it is still uncertain whether such lesions could result in neurodevelopmental delay. With the help of fMRI, accurate assessment of microstructural changes of the brain and neurological function becomes feasible and it is possible to give a prognosis for these lesions. We therefore performed this meta-analysis to determine whether harmful prenatal hemodynamics and/or the surgical procedure affect neurological performance.

## METHODS

### Electronic search

We performed an electronic search of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials and the World Health Organization clinical trials registry center, without language restriction, in December 2013, using the following search strategy: 'heart defects, congenital [MeSH Terms] OR congenital heart disease' AND 'brain OR neurology OR neurological OR cerebral OR cerebrum' AND 'DTI OR MRI OR MRS OR diffusion tensor imaging OR magnetic resonance image OR magnetic resonance spectroscopic'. For abstracts and unpublished studies, e-mails were sent to authors requesting more detailed information.

### Study selection

Studies retrieved from the electronic search were screened preliminarily by title and/or abstract. Complete manuscripts of potentially relevant studies were then retrieved and assessed according to inclusion and exclusion criteria.

Studies analyzing the delay in neurological development in newborns with CHD were included if they met all of the following criteria: 1) patients were diagnosed as having CHD by echocardiography or other diagnostic methods, such as MRI or computed tomography angiography; 2) controlled study with neonatal CHD group and healthy control group; 3) contained at least one of the outcome measures; 4) neonatal MRS was performed.

Studies analyzing the impact of cardiac surgery were included if they met all of the following criteria: 1) patients with confirmed diagnosis of CHD and cardiac surgery; 2) both preoperative and postoperative fMRI results in the same individuals within the cohort, for comparison an individual's postoperative levels with their own baseline levels ('self-control'); 3) contained at least one of the outcome measures.

Exclusion criteria for both types of analysis were: 1) comparison not focused on neurological evaluation; 2) overlap of patients with those in other studies.

### Data collection and quality assessment

Following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[11], two investigators (Y.L., S.Y.) assessed independently the eligibility of studies using identical data collection charts. In cases of disagreement, a third reviewer (K.Z.) was consulted for a final decision. Studies that met the inclusion criteria were selected for further analysis, quality assessment being carried out according to the quality assessment guidelines for non-randomized controlled studies by Deeks *et al.*[12] and the MOOSE guideline[11].

### Outcome measures

Among CHD cases, neurodevelopmental delay in the neonatal period was measured by the Dav for gray matter, Dav for white matter, overall Dav, fractional anisotropy (FA) for white matter, NAA/choline (Cho) ratio for the whole brain and Lac/Cho ratio for the whole brain. The potential impact of cardiac surgery on brain metabolism was evaluated using the difference of overall Dav and FA for white matter before and after surgery, as well as the differences of NAA/Cr and NAA/Cho before surgery and both immediate term and short term postoperatively, with immediate term being considered as 3–5 days after surgery and short term as 10–20 days following the procedure. We used these measures to evaluate the neurological development of newborns with CHD to determine whether any impact was caused by CHD itself or by the cardiac surgery.

### Statistical analysis

The Q statistic was used on the research effect size to evaluate heterogeneity. If the results were not significantly heterogeneous ($I^2 < 50\%$), count data were analyzed using a fixed-effect model (Peto's method). If significant heterogeneity was detected ($I^2 \geq 50\%$), the random-effect model

was used. Meta-regression was performed, using STATA 11.0 (Stata Corp., College Station, TX, USA), to determine whether critical CHD subtypes (transposition of the great arteries (TGA), single ventricle and 'mixed' cases (some studies including various types of critical CHD)) or publication year were potential factors related to heterogeneity.

Begg's funnel plot was presented using STATA 11.0 to evaluate the possibility of publication bias. An asymmetrical plot would indicate the existence of publication bias. Additionally, we measured the funnel plot asymmetry using Egger's test. $P < 0.05$ was considered statistically significant.

Pooled analysis of selected studies was performed with Revman 5.1.1 (Cochrane Library). Pooled odds ratios and 95% CIs were determined. Continuous data were analyzed using weighted standardized mean difference (std mean difference) and 95% CI to account for differences in the variability of observations between the included studies. All continuous variables were calculated as mean ± SD.

Sensitivity analyses were performed by subgroup analysis to evaluate the bias from different types of CHD, and we carried out additional subgroup analysis according to type of CHD (TGA alone, SV alone and mixed cases) to identify their direction and magnitude of statistical significance in the findings of the overall analysis.

## RESULTS

### Study evaluation

In total, 937 citations were retrieved by searching the databases (Figure 1). After reading titles and abstracts, 922 citations were excluded, leaving 15 articles for further consideration. Among these, on reading the full text, eight articles were excluded, including four focusing on brain volume and metrics[13–16], two on the method of constructing three-dimensional MRI images and white-matter injury in routine MRI, which provided no useful indicators among fMRI evaluation[17,18], and two studies of adults[19,20]. One additional study was included by manual retrospective search after reading related publications. Overall, we included in the meta-analysis eight articles containing nine studies that met our inclusion and exclusion criteria[21–28]: six studies[21–26] that evaluated neurodevelopmental delay in newborns with CHD and three[22,27,28] that evaluated the potential impact of cardiac surgery. This gave a total of 312 patients (219 newborns with CHD and 93 healthy controls), of whom 36 had undergone both preoperative and postoperative fMRI. The quality of all included articles was acceptable, describing in detail factors that might have influenced the prognosis and the method of allocation. Table 1 summarizes the basic characteristics of the studies included and Table 2 describes the quality evaluation of these studies.

### Neurodevelopmental delay in newborns with CHD

For overall Dav, 208 cases in four studies[22–25] were included, with 146 cases in the CHD group and 62 healthy controls. Significant heterogeneity was detected across studies ($I^2 = 75\%$), and a random-effect model was adopted. The CHD group had higher overall Dav compared with the control group (std mean difference = 1.39 (95% CI, 0.70–2.08), $P < 0.0001$) (Figure 2).

The comparison of mean Dav of gray matter included 177 cases in three studies[21,23,24], with 126 cases in the CHD group and 51 healthy controls. There was no significant heterogeneity across studies ($I^2 = 32\%$), and a fixed-effect model was applied. The mean Dav for gray matter was increased in the CHD group compared with controls (std mean difference = 0.67 (95% CI, 0.34–1.01), $P < 0.0001$) (Table 3).

The comparison of mean Dav of white matter included 177 cases in three studies[21,23,24], with 126 cases in

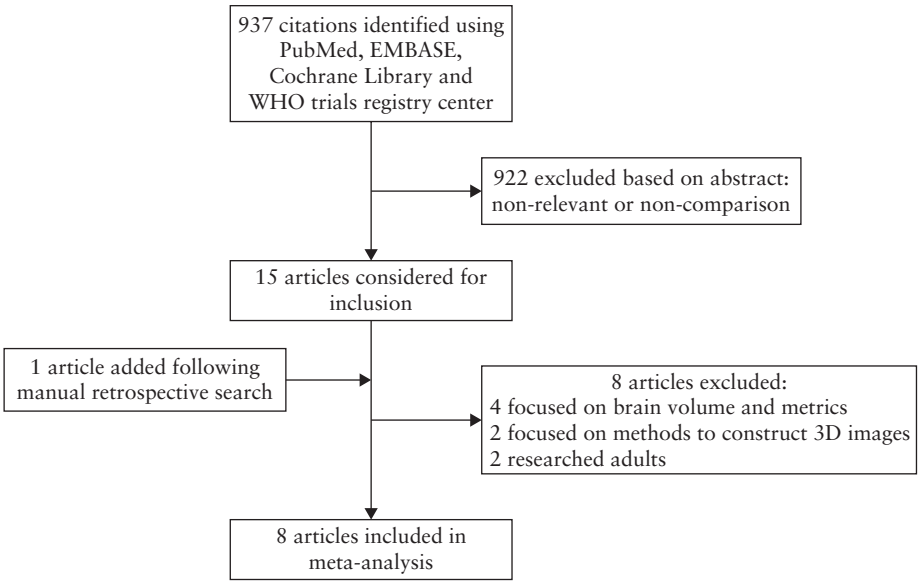


**Figure 1** Flow diagram summarizing study selection process. 3D, three-dimensional; WHO, World Health Organization.

 

**Table 1** Main characteristics of articles included in the meta-analysis

| *Study* | *Origin of population* | *Type of study* | *Study cohort* | *Cases/ ctrls* (n) | *ROI* (n) | *BW (kg) (cases/ctrls)* | *GA at birth (wks) (cases/ctrls)* | *Postnatal days at first MRI (cases/ctrls)* | *Days from surgery to second MRI* |
|---|---|---|---|---|---|---|---|---|---|
| Makki (2013)[22]* | Switzerland | Case & self control | TGA | 15/11 | 3 | 3.38 ± 0.45/ 3.47 ± 0.42 | 39.0 ± 1.1/ 39.0 ± 1.0 | 8 ± 6/ 26 ± 5 | 14 ± 6 |
| Sethi (2013)[21]† | Canada & USA | Case–control | SV | 36/16 | 7 | 3.19 ± 0.47/ 3.64 (2.89–5.56) | 38.8 ± 1/ 40.1 ± 0.8 | 5 (1–13)/ 6.8 ± 3.5 | — |
| Abdel Raheem (2012)[23] | Saudi Arabia | Case–control | Mixed | 52/15 | 7 | 3.24 ± 0.34/ 3.40 ± 0.23 | 38.7 ± 1.2/ 38.2 ± 1.1 | 5.6 ± 2.1/ 4.7 ± 1.9 | — |
| Shedeed (2011)[24] | Egypt | Case–control | Cyanotic CHD | 38/20 | 7 | 3.03 ± 0.36/ 3.58 ± 0.43 | 39.1 ± 1.8/ 38.3 ± 1.5 | 3.5 ± 6.2/ 2.8 ± 4.6 | — |
| Miller (2007)[25] | USA | Case–control | TGA & SV | 41/16 | 7 | 3.30 (3.00–3.58)/ 3.64 (3.36–4.08) | 39.1 (38.2–40.0)/ 39.6 (39.2–40.5) | 5 (3–6)/ 7 (4–9) | — |
| Park (2006)[26] | Korea | Case–control | TGA | 16/15 | 2 | 3.2 (2.1–3.9)/ — | 40 (38–41)/ (38–42) | Range, 3–6 | — |
| Miller (2004)[27] | USA | Self control | TGA | 10 | 3 | 4.02 (2.64–4.60) | 39.9 (39–41) | 6 (2–9) | 17.5 (14–25) |
| Ashwal (2003)[28] | USA | Self control | Mixed | 11 | 2 | — | — | On day of surgery | Range, 2–5 |

Only the first author of each study is given. Data are given as *n*, mean ± SD or mean (range), unless stated otherwise. No case of transposition of the great arteries (TGA) underwent balloon atrial septostomy. There was no difference in gestational age (GA) at birth between congenital heart disease (CHD) and healthy groups. *Comparison between preoperative CHD cases and healthy controls, and also between preoperative and postoperative CHD cases. †Compared with healthy cohort published previously[40]. BW, birth weight; ctrls, controls; MRI, magnetic resonance image; ROI, regions of interest; SV, single ventricle; wks, weeks.

the CHD group and 51 healthy controls. Significant heterogeneity across studies was detected ($I^2 = 74\%$), so a random-effect model was applied. The mean Dav for white matter was higher in the CHD group compared with controls (std mean difference = 0.21 (95% CI, 0.18–0.24), $P < 0.00001$) (Table 3).

The comparison of mean FA of white matter included 260 cases in five studies[21–25], with 182 cases in the CHD group and 78 healthy controls. There was significant heterogeneity across studies ($I^2 = 66\%$), and a random-effect model was adopted. The CHD group had a lower mean FA of white matter than did the control group (std mean difference = −1.43 (95% CI, −1.95 to −0.91), $P < 0.00001$) (Figure 3).

The comparison of mean NAA/Cho included 296 cases in six studies[21,23–26], with 199 cases in the CHD group and 97 healthy controls. There was significant heterogeneity across studies ($I^2 = 12\%$), and a fixed-effect model was applied. The mean NAA/Cho was lower in the CHD group than in the control group (std mean difference = −1.09 (95%CI, −1.35 to −0.83), $P < 0.00001$) (Figure 4).

The comparison of mean Lac/Cho included 182 cases in three studies[23–25], with 131 cases in the CHD group and 51 healthy controls. There was significant heterogeneity across studies ($I^2 = 80\%$), and analysis was by a random-effect model. The two groups were significantly different (std mean difference = 1.20 (95% CI, 0.41–1.99), $P = 0.003$) (Table 3).

### Potential impact of cardiac surgery

For the comparison of overall Dav before and after surgery, only one study (15 cases) was eligible for inclusion[22]. No significant difference was found between the preoperative and postoperative measurements (std mean difference = −0.18 (95% CI, −0.89 to 0.54), $P = 0.63$).

For the comparison of FA of white matter before and after surgery, only one study (15 cases) was included[22]. The mean postoperative FA for white matter was not significantly different from the preoperative measurement (std mean difference = 0.49 (95% CI, −0.24 to 1.21), $P = 0.19$).

The comparison of NAA/Cr included two studies in one article[28], with 11 cases measured preoperatively, immediate term postoperatively (3–5 days postoperatively) and short term postoperatively (10–20 days postoperatively). There was a significant difference in mean NAA/Cr between the preoperative measurement and the immediate-term postoperative measurement (std mean difference = 0.97 (95% CI, 0.09–1.87), $P = 0.03$). There was no significant difference in mean NAA/Cr between the preoperative and the postoperative short-term measurement (std mean difference = −0.20 (95% CI, −1.04 to 0.64), $P = 0.64$).

The comparison of NAA/Cho included three studies[27,28], with 21 cases measured preoperatively, 11 cases immediate term postoperatively and 21 cases short term postoperatively. There was a significant difference in mean NAA/Cho between the preoperative measurement and the immediate-term postoperative measurement (std mean difference = 0.97 (95% CI, 0.07–1.86), $P = 0.03$). There was no heterogeneity analysis because only one study[28] was involved in this evaluation. There was no significant difference in mean NAA/Cho between the preoperative measurement and the short-term postoperative measurement (std mean difference = −0.40 (95% CI, −1.02 to 0.22), $P = 0.21$).

**Table 2** Main quality evaluation of studies included in the meta-analysis

| *Study* | *Blinding of researchers* | *Attempt to balance groups for key factors* | *Prognostic factors considered* | *Case-mix adjustment* | *Attrition assessment* |
|---|---|---|---|---|---|
| Makki (2013)[22] | One of two researchers blinded to neuroimaging results and processing | All included cases within same strategy matched for age and surgical procedure | Reported GA, weight, administration, surgical procedure, MRI days and subtype characteristics | Yes | None |
| Sethi (2013)[21] | Researchers blinded to neuroimaging results | All included cases from same research center with age-matched controls | Reported GA, BW, administration, surgical procedure, Apgar score, MRI days and subtype characteristics | None | N/A |
| Abdel Raheem (2012)[23] | Not reported | All included cases from same research center with age- and sex-matched controls; no history of prenatal or perinatal complications | Reported GA, BW, administration, surgical procedure, Apgar score, MRI days and subtype characteristics | None | N/A |
| Shedeed (2011)[24] | Not reported | All included cases from same research center with age-, sex- and gestational-week-matched controls; completed a full history through parental questionnaire interview | Reported GA, BW, administration, surgical procedure, MRI days and subtype characteristics | None | N/A |
| Miller (2007)[25] | Researchers blinded to neuroimaging results | All included cases from same research center with age-matched controls | Reported GA, BW, administration, surgical procedure, MRI days and subtype characteristics | Yes | N/A |
| Park (2006)[26] | Not reported | All included cases from same research center with age-matched controls | Reported GA, BW, administration, surgical procedure, MRI days and subtype characteristics | None | N/A |
| Miller (2004)[27] | Researchers blinded to neuroimaging results | All included cases from same research center matched for gestational week and surgical procedure | Reported GA, BW, administration, surgical procedure, Apgar score, MRI days and subtype characteristics | None | None |
| Ashwal (2003)[28] | Researchers blinded to group assessment of participants | All included cases from same research center matched for gestational week | Reported administration, surgical procedure, MRI days and subtype characteristics | None | None |

Only the first author of each study is given. The quality of all articles was acceptable. For all studies, the case allocation method involved both doctors and patients. BW, birth weight; GA, gestational age; MRI, magnetic resonance imaging; N/A, not applicable (because study was cross-sectional).

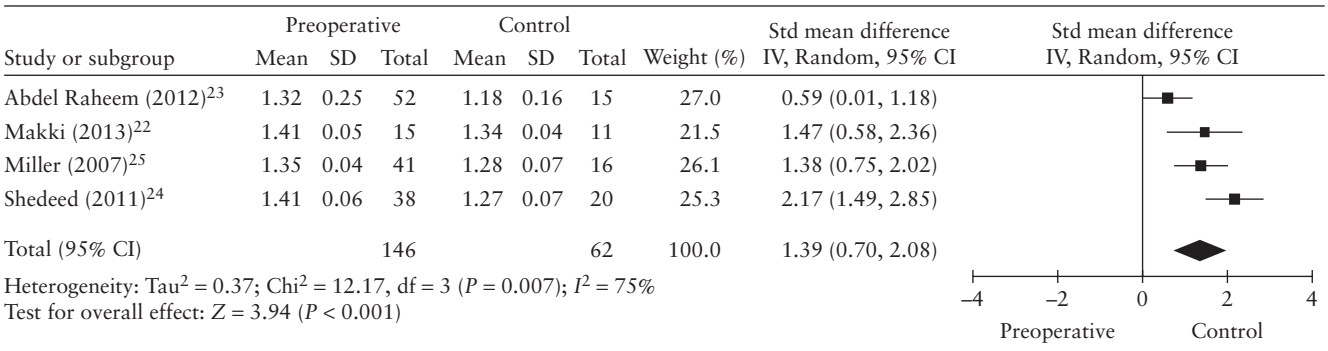


**Figure 2** Forest plot for comparison of overall average diffusivity in neonates with congenital heart disease preoperatively and in healthy controls. Only the first author of each study is given. df, degrees of freedom; IV, inverse variance.

 

**Table 3** Summary of data from comparison between preoperative congenital heart disease (CHD) cases and healthy controls

| *Variable* | *Summarized std mean difference (95% CI)* | *Test for overall effect* | | *Test for heterogeneity* | | |
|---|---|---|---|---|---|---|
| | | Z | P | $\chi^2$ | P | $I^2$ *(%)* |
| Dav: gray matter | 0.67 (0.34, 1.01) | 3.93 | < 0.0001* | 2.93 | 0.23 | 32 |
| Dav: white matter | 0.21 (0.18, 0.24) | 13.32 | < 0.00001* | 7.77 | 0.02† | 74 |
| Lactate/choline | 1.20 (0.41, 1.99) | 2.98 | 0.003* | 10.02 | 0.007† | 80 |

*Suggested significant difference between preoperative CHD cases and healthy controls. †Suggested significant heterogeneity among enrolled studies, and using random-effect model for meta-analysis. Dav, average diffusivity, from diffusion tensor imaging; std, standardized.

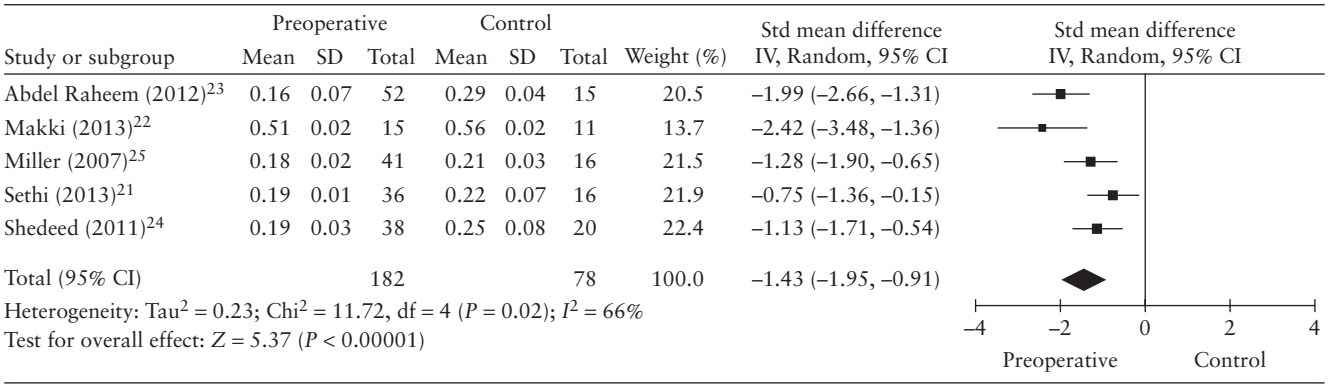


**Figure 3** Forest plot for comparison of fractional anisotropy of white matter in neonates with congenital heart disease preoperatively and in healthy controls. Only the first author of each study is given. df, degrees of freedom; IV, inverse variance.

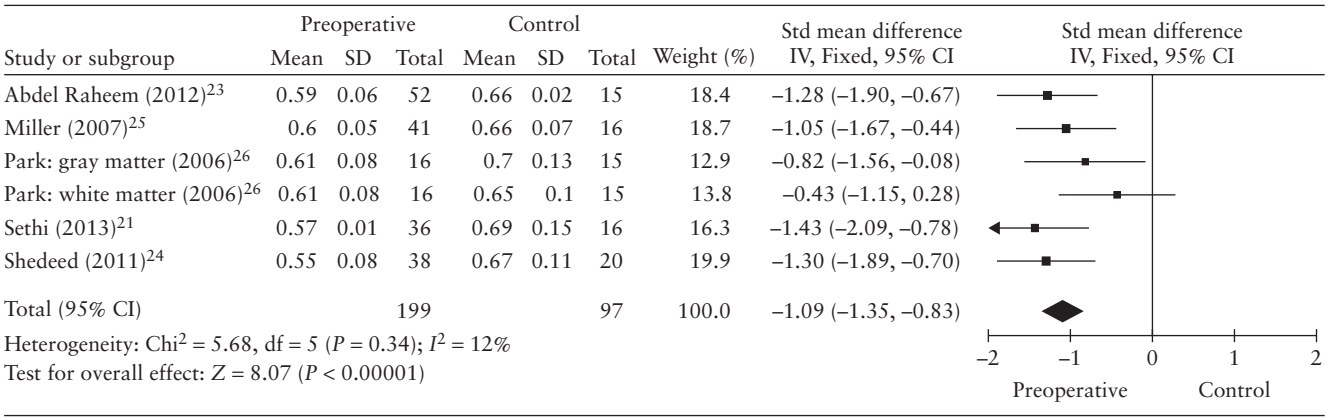


**Figure 4** Forest plot for comparison of N-acetylaspartate/choline in neonates with congenital heart disease preoperatively and in healthy controls. Only the first author of each study is given. df, degrees of freedom; IV, inverse variance.

There was no significant heterogeneity across these studies ($I^2 = 36\%$) and analysis was by a fixed-effect model. There was a significant difference between these subgroups comparison ($P = 0.01$) (Figure 5).

### Sensitivity analysis

Sensitivity analysis was done using subgroup analysis of the cases with TGA alone, SV alone and mixed cases, which confirmed both the direction and magnitude of statistical significance in the findings of the overall analysis. To determine whether the observed high levels of variability between studies (i.e. heterogeneity) was due to different types of CHD, we carried out additional subgroup analysis according to CHD type: studies with each type of CHD were pooled and these results confirmed the direction and magnitude of statistical significance as determined by the overall analysis.

### Meta regression

As the type of CHD might impact neurological performance, we performed a meta-regression to identify whether critical CHD subtypes contributed to the heterogeneity. The results showed that CHD subtype was not responsible for the heterogeneity of the overall Dav

 

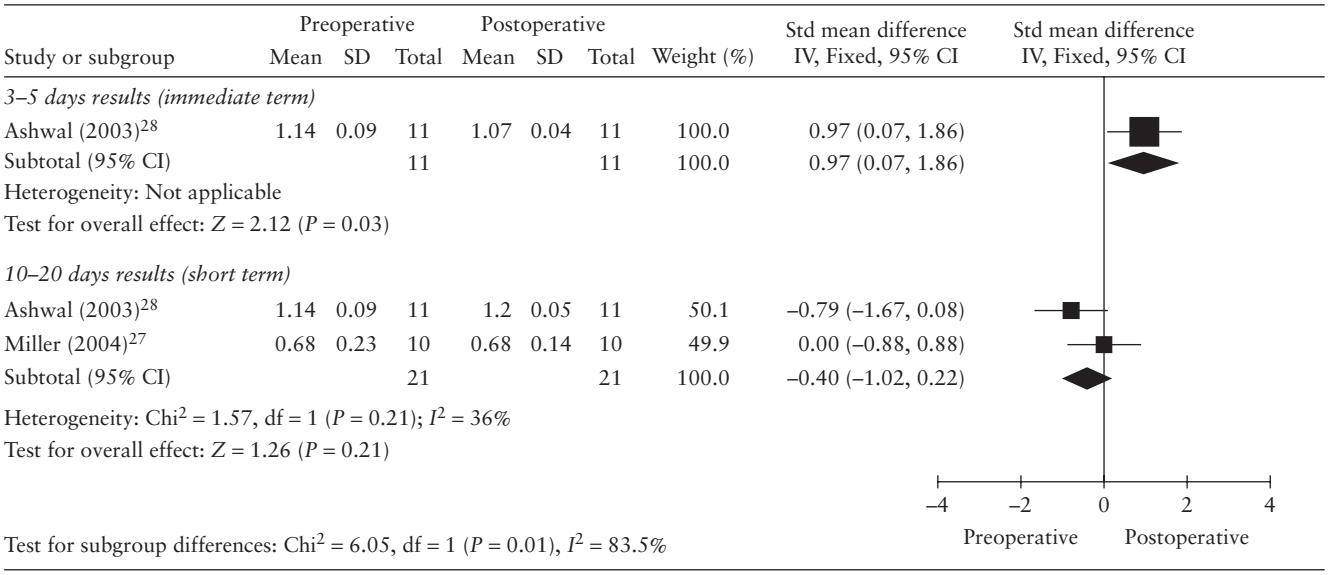


**Figure 5** Forest plot for comparison of N-acetylaspartate/choline in neonates with congenital heart disease preoperatively and postoperatively. Only the first author of each study is given. df, degrees of freedom; IV, inverse variance.

evaluation (standard error (SE) = 0.49 (95% CI, −2.04 to 2.17), $P = 0.906$, Figure 6a), the Dav of white matter evaluation (SE = 0.37 (95% CI, −5.16 to 4.15), $P = 0.40$, Figure 6b) or the FA of white matter evaluation (SE = 0.40 (95% CI, −1.05 to 1.50), $P = 0.62$, Figure 6c). As the CHD cases included in the Lac/Cho evaluation were of mixed type, no meta-regression was performed for this comparison. Additionally, the publication year of studies was taken into account in the meta-regression analysis, and was found not to contribute to heterogeneity.

### Publication bias

To assess the publication bias of studies, Begg's funnel plot and Egger's test were applied. The funnel plot was symmetrical, indicating the absence of publication bias (Figure 7), and this was supported by the Egger's test result ($t = 2.01$, $P = 0.115$) for the NAA/Cho evaluation between CHD cases and healthy controls. Egger's test also showed no publication bias in overall Dav evaluation ($t = 0.75$, $P = 0.533$) and in FA evaluation ($t = -2.05$, $P = 0.133$) between CHD cases and healthy controls. As there were only a few studies pooled in the other evaluations, no publication bias analysis was carried out.

## DISCUSSION

Abnormal motor and cognitive development (associated with white-matter injury and periventricular leukomalacia changes) has been observed in preterm newborns affected by hypoxia and injury during delivery[29]. CHD patients are also affected by hypoxia, which may lead to similarly compromised neurological development[30]. A meta-analysis on conventional MRI changes[31] suggested an association between CHD and neurodevelopmental delay, and that infants with CHD had an increased risk for brain lesions and neurodevelopmental delay independent of surgery, but it failed to identify the precise time of onset of brain injury (i.e. preoperative or postoperative) and did not include fMRI results. In this meta-analysis we compared brain development between CHD cases and healthy controls during the neonatal period, and evaluated the impact of cardiac surgery on neurological performance.

Only a limited number of studies matched our inclusion criteria, especially for the perioperative evaluation of fMRI, and sample size was small in some comparisons. Therefore, we pooled the results for all types of CHD, as has been done in previous meta-analyses[4,31]. Moreover, heterogeneous results were identified across studies. To check for heterogeneity, meta-regressions were performed; while we failed to identify its source, the results proved that neither the type of CHD nor the publication year of the study made any contribution to heterogeneity. Furthermore, subgroup analysis according to CHD type (including TGA, single ventricle and mixed cases) confirmed the same direction and magnitude of statistical significance as was found by the overall analysis. Although it has been reported that the incidence of brain abnormalities differs between different types of CHD[32], we did not find significant differences between different types of CHD in fMRI evaluation compared with normal controls. Further investigation is needed, and the results of this meta-analysis should be interpreted with caution. There is also a possibility that there were brain injuries peripartum in CHD cases, but most studies do not report these data.

### Evaluation of preoperative neurological performance in neonates

DTI and MRS can measure quantitatively brain development and injury within a few days after delivery and surgery. Previous studies have reported a correlation between fMRI evidence of impairment and both

 

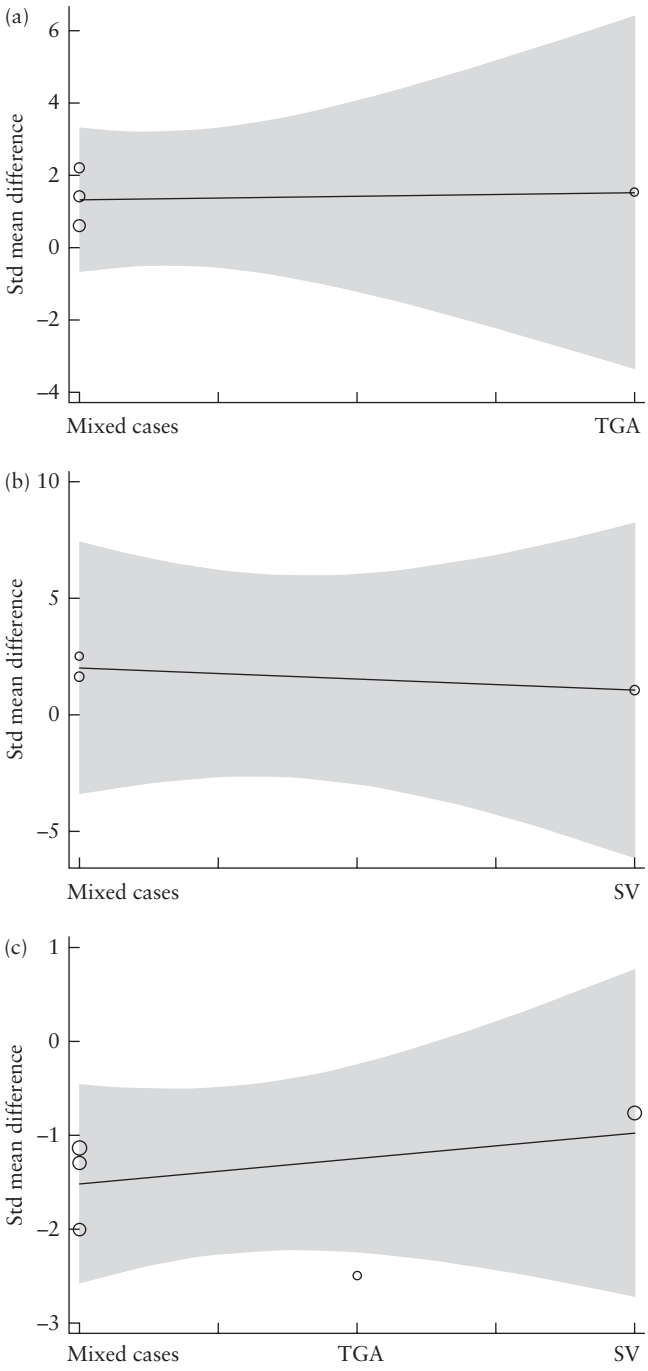


**Figure 6** Meta regression showed that congenital heart disease subtype made no contribution to heterogeneity. Evaluation of: (a) overall average diffusivity; (b) average diffusivity of white matter; (c) fractional anisotropy of white matter. Circles represent studies. Std, standardized; SV, single ventricle; TGA, transposition of the great arteries.

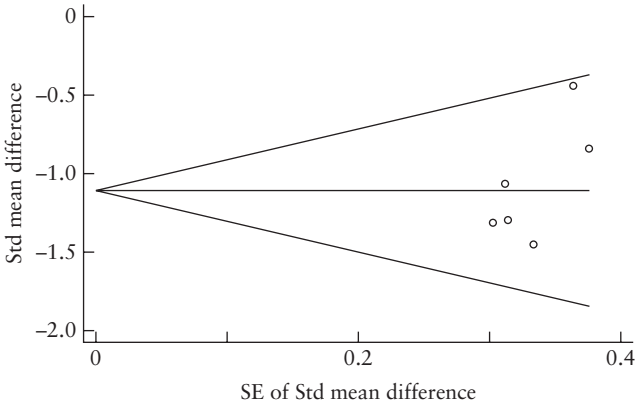


**Figure 7** Begg's funnel plot of included trials of N-acetylaspartate/choline evaluation, with pseudo 95% CIs: *y*-axis represents effect estimate for each study under the outcome; *x*-axis represents standard error (log(effect estimate)). Each circle represents a study and the distance between each and the *x*-axis suggests bias in each study. The absence of any dots for completing a symmetrical structure suggests some publication bias.
SE, standard error; Std mean difference, standardized mean difference.

adverse neurodevelopmental outcome and delayed brain maturation[6–8,22]. In this meta-analysis, we identified impaired performance of the neurological system in neonates with CHD, who had lower NAA/Cho ratio and NAA level, but higher Lac/Cho ratio and Lac level, compared with controls. NAA is predominantly a neuronal biomarker and decreased NAA level is related to glial pathological changes observed in fetuses and newborns with CHD. Cheong *et al.* reported that Lac/Cho was a sensitivity biomarker that elevated significantly in hypoxia-ischemic injury[33]. Moreover, the results of Dav and FA also showed that neurodevelopmental impairment was present extremely early after delivery. The abnormal brain microstructure and metabolism shortly after delivery in CHD cases is consistent with previously published evidence that impaired brain development occurred *in utero*, possibly related to impaired cerebral oxygen and substrate delivery prenatally[34,35]. Additionally, regarding the metabolism and diffusion profile, studies showed that 55% of newborns with hypoplastic left heart syndrome were complicated with microcephaly and 21% suffered from immature cortical mantle, despite adaptation by cerebral vasodilatation during fetal development[34]. Overall, this pattern is consistent with diminished antegrade fetal cerebral blood flow with diminished oxygen and nutrient delivery that leads to delayed brain development.

## Potential impact of cardiac surgery and cardiopulmonary bypass

Advances in cardiac surgical techniques and perioperative intensive care have improved survival rates in newborns with CHD[16,36]. Several studies on postoperative lesions or white-matter injury have confirmed that certain abnormalities result from surgery and cardiopulmonary bypass, but conventional MRI is not sufficiently accurate to detect such the subtle changes present immediately after surgery. With the help of fMRI, even very slight changes in brain microstructure and metabolism can be detected immediately after surgery, with higher sensitivity than is normally possible with conventional MRI. Moreover, for the same reasons, continuous follow-up even at an interval of a few days may detect changes which would not be recognized using conventional MRI. In the studies included in this meta-analysis, postoperative

fMRI evaluation was performed 3–5 days postoperatively (immediate term) and, to determine whether there was recovery later, 10–20 days postoperatively (short term), providing accurate information of brain injury associated with cardiopulmonary bypass and surgery. We confirmed changes in cerebral metabolites and DTI evaluation immediate-term postoperatively. However, postoperative short-term re-evaluation showed recovery to preoperative baseline. Decreased NAA/Cho after surgery indicated a detrimental effect of intraoperative or postoperative events on cerebral cellular metabolism, which means the metabolic profile was impaired shortly after the cardiac surgical procedure. However, results from DTI and MRS in individual newborns comparing the preoperative and postoperative measurements revealed some cases with intact cerebral integrity and function after surgery. In Miller *et al.*'s cohort of newborns with TGA, perioperative indices of cardiac function and cardiopulmonary bypass were not significantly associated with three-dimensional MRS metabolite ratios[27], suggesting that preoperative brain injury plays a more important role in predisposing to impaired cerebral cellular metabolism. This differs considerably from the high occurrence of new lesions in the early postoperative period found by Mahle *et al.* in a cohort of patients with single ventricle[37].

In this meta-analysis, we found that, while cardiac surgery and cardiopulmonary bypass caused a certain amount of damage to the brain and disturbed the metabolite levels, this was limited to only a short period of time, as the level of diffusion and metabolism restored to baseline levels within a short period of time. The neurodevelopmental delay in cases of critical CHD was a result of abnormal fetal hemodynamics, suggesting that the origin of such injury was mainly preoperative. Therefore, it is recommended to treat for cerebral protection during both pregnancy and surgery. Intervention methods to improve fetal circulation have been investigated; these could provide the fetus with opportunities to rebuild its circulation[38], and have been found to protect the heart, with better prognosis for the pregnancy[39]. As the brain injuries associated with CHD are likely to be due mainly to harmful hemodynamics, such a method that improves the fetal circulation would be promising as a means to provide some protection for the brain also. Information regarding brain maturation is essential for determining the right time for intervention[25]. Since our meta-analysis found that impaired brain metabolism and microstructures could progress to neurodevelopmental delay shortly after birth, we recommend maintenance of normal circulation to improve oxygen supply during fetal life, once critical CHD is diagnosed, to protect critical CHD cases from severe neurodevelopmental delay.

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