Cognitive and behavioral outcome in Dutch children after neonatal surgery for congenital heart disease

Master's thesis

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Voorwoord

Met gepaste trots presenteer ik bij deze mijn masterthesis 'Cognitive and behavioral outcome in Dutch children after surgery for congenital heart disease.' In mijn masterthesis wordt onderzoek gedaan naar hoe kinderen met een vernauwde of onderbroken aortaboog, met of zonder te kleine linkerhartkamer, op de leeftijd van 2 en 5 jaar functioneren op cognitief en gedragsmatig vlak in vergelijking tot hun 'normaal' ontwikkelende leeftijdsgenoten. Daarnaast wordt er gekeken naar voorspellende factoren op het gebied van gedrag en cognitie.

Mijn masterthesis heeft mij de mogelijkheid geboden me verder te verdiepen in de invloed van complex medisch handelen op uitkomsten op latere leeftijd. Het was erg interessant me in te mogen lezen in een onderwerp waarover ik van tevoren nog niet zoveel kennis had. Mijn medische kennis is na het schrijven van mijn thesis sterk vergroot!

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Ik wens u veel leesplezier toe.

Anne Jacobs

COGNITIVE AND BEHAVIORAL OUTCOME IN DUTCH CHILDREN
AFTER NEONATAL SURGERY FOR CONGENITAL HEART DISEASE

Abstract

More and more children with a congenital heart disease [CHD] survive, as diagnosis and surgical possibilities improve. Along with these improvements, interests in longer-term cognitive and behavioral outcomes of these children increase. The aim of the present study was to map the cognitive and behavioral development of children with a coarctation or interruption of the aortic arch with or without hypoplastic left heart syndrome. This longitudinal follow-up study used participants from an earlier RCT and examined cognition with the Bayley-III-NL at age 24 months (n = 32), and the WPPSI-III-NL at age five years (n = 22). Behavior was examined with the CBCL/1.5-5 at both 24 months and five years and with the C-TRF at five years. Results showed that the cognition of CHD children was in the normal range at both 24 months and five years, but that their processing speed was significantly lower. According to their parents (at both 24 months and five years) and teachers, the CHD children show less anxious/depressed behavior then their typically developing peers. Teachers report higher attention problem scores in these children. Bayley-III-NL cognition score was a significant predictor of WPPSI-III-NL FSIQ score. More attention problems according to parents at age five predict more attention problems according to teachers at age five. Higher attention problem scores reported by teachers predict a lower FSIQ score at age five. It can be concluded that the behavioral and cognitive outcome in this sample is relatively positive. It is important to closely monitor the attention problems in CHD children, as they seem to affect cognitive development.

Keywords: Congenital heart disease – development - behavior – cognition – attention – processing speed

Cognitive and behavioral outcome in Dutch children after neonatal surgery for congenital heart disease

Twenty-eight percent of the congenital anomalies concern congenital heart disease [CHD], which means approximately 1250 children per year are born with a CHD in the Netherlands (Dolk, Loane, & Garne, 2011; Van der Linde et al., 2011). CHD can be defined as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" (Mitchell, Korones, & Berendes, 1971). More and more of these children survive into adulthood, due to major improvements in, for example, diagnosis and surgical possibilities (Brosig, Mussatto, Kuhn, & Tweddell, 2007; Tweddel et al., 2002). Together with the chance of survival, interests in long-term effects such as cognitive and behavioral outcomes increase.

The present study focuses on cognitive and behavioral outcomes of children born with either coarctation or obstruction of the aortic arch, with or without severe underdevelopment of the left heart (hypoplastic left heart syndrome [HLHS]). Due to the complexity of their disorder, these children need surgery for correction or palliation of their injury soon after delivery. As they undergo surgery in the neonatal period, they might be at greater risk of brain injury compared with older children, as white matter is still developing and therefore more vulnerable to acute changes in perfusion and oxygenation (Rezaie & Dean, 2002).

Although brain damage can appear as a negative side effect of complex cardiac surgery, multiple studies show that brain injury in may already be present before surgery (Algra et al., 2014; Galli et al., 2004; Mahle et al., 2002; Miller et al., 2007). This presumes that it might be explained by impaired cerebral oxygen delivery in utero, which is specifically observed in the heart diseases represented in the present study (Algra et al., 2013; Donofrio et al., 2013; Miller et al., 2007). Even though neurological damage, obtained in utero or perioperative, is associated with adverse cognitive and behavioral outcomes, it is not possible to directly connect neurological deviations to cognitive and behavioral disadvantages.

Multiple studies show that children suffering a CHD have lower IQ scores than the normal population (Griffin, Elkin, & Smith, 2003; Mahle et al., 2005; Majnemer et al., 2008; Miatton, De Wolf, Francois, Thiery, & Vingerhoets, 2007a; Uzark et al., 1998). Research of Hülser, Dubowy, Knobl, Meyer and Schölmerich (2007) showed that children that underwent

surgery for CHD have worse cognitive development at preschool age. A meta-analysis of Karsdorp, Everaerd, Kindt and Mulder (2007) found that the cognitive function depended on the severity of the heart disease, especially with regard to performal IQ. Especially children with HLHS and transposition of the great arteries [TGA], a part of the population of the present study, suffered from significantly lower cognitive functioning. In contrast, Brosig, Mussatto, Kuhn and Tweddell (2006) found no significant differences in children with HLHS and TGA compared to population norms. Studies focusing on the cognitive development over a longer period in childhood are scarce, as most are cross-sectional. The results of the few longitudinal studies are not unanimous. A study by Creighton et al. (2007) suggests an upward trend in mental scores from the age of two years old to intelligence scores at the age of five years old. Results from the meta-analysis by Karsdorp et al. (2007) indicate that cognitive functioning remains relatively stable across the years.

Next to the above-mentioned cognitive effects, there are many studies highlighting the behavioral outcomes in children with a CHD. CHD children would have more externalizing problems, in comparison with typically developing children (Miatton et al., 2007b; Schillingford et al., 2008). More specifically, CHD children have, according to the literature, more potential to develop attention and hyperactivity problems than their typically developing peers (Hansen et al., 2012; Schillingford et al., 2008; Sistino et al., 2013; Yamada et al., 2013). Schillingford and colleagues (2008) found out that CHD children suffer three to four times as much attention problems and hyperactivity at school age, reported by teachers as well as parents. Yamada and colleagues (2013) reported that no less than 29% of the children with a CHD in their study met the criteria for positive screening for ADHD, against 3% of the healthy control group. Also, more internalizing problems are indicated by many studies (Hövels-Gürich et al., 2002; Majnemer et al., 2008; Miatton et al., 2007b).

There are some studies actually that nuance the above-mentioned results. In a study of Hülser et al. (2007), no differences were found concerning behavioral problems between the CHD group and the reference group. Karsdorp and colleagues (2007) found that only older children suffered more behavior problems than typically developing children without CHD. Another study reports on the fact that the amount of behavioral problems depends on the type of heart disease, with more problems for the HLHS group than for the TGA group (Brosig et al.,

2007). Again, few studies focusing on behavioral outcomes in CHD children applied a longitudinal design.

The aim of the present study is to determine whether cognitive and behavioral outcomes of children with either coarctation or interruption of the aortic arch with or without HLHS who had a cardiac surgery including aortic arch reconstruction in the first three months of their lives, differ from typically developing [TD] children in the preschool and early childhood age. As mentioned, not many studies targeted the cognitive and behavioral development in a longitudinal way. Therefore, the present study takes a closer look at the relationship between cognitive development at two years old and intelligence at the age of five years. The development of behavior between two and five years is also studied. Although many studies focused on cognitive and behavioral outcomes of CHD children, the relation between cognition and behavior in these children remains unknown. That's why this study also takes a closer look at the relation between behavior and cognition.

Based on previous literature, it is hypothesized that these children show worse cognitive development than TD children at age two and a lower intelligence at age five. Cognitive development at two years is expected to be an important predictor for intelligence at age five. Concerning behavior, it is expected that children with a CHD show, according to their primary caregivers and teachers, more internalizing problems at age two and age five than TD children. Also, more attention problems are expected. On the longer-term, it is expected that the attention problems according to parents, predict attention problems according to teachers. As regards the relation between children's behavior and cognition, it is expected that more attention problems are associated with lower intelligence scores.

Method

Participants

Participants were originally recruited for a randomized controlled trial [RCT] comparing the cerebral effects of two different perfusion techniques during complex neonatal cardiac surgery (Algra et al., 2014). All neonates born between January 2009 and May 2012 qualifying for aortic arch reconstruction at the Wilhelmina Children's Hospital (University Medical Center Utrecht, The Netherlands) were assessed for enrollment. Children older than four months, children with high suspicion of a genetic syndrome and children with specific medical conditions were excluded at the time. The group originally consisted of 36 patients.

The present study focuses on the 24-month and 5-year follow-up of these patients. At 24 months, 32 patients completed the Bayley-III-NL. One patient died a few weeks after discharge, one patient withdrew and two patients weren't able to participate due to substantial physical or mental limitations. At 5-year follow-up, 22 patients completed the WPPSI-III-NL. One patient died after later cardiac surgery, one additional patient withdrew, five patients didn't reach the age of five years yet and some children were not able to complete all scales of the WPPSI-III-NL, which made it impossible to calculate a FSIQ score. Some of the children were tested elsewhere, where their parents and teachers didn't fill out a CBCL/1.5-5 and C-TRF questionnaire. Patient characteristics are shown in Table 1.

Table 1

Perinatal and demographic characteristics of the CHD children in the original and follow-up study

N	36
Male sex, N (%)	28 (77.8)
Gestational age (weeks)	
M	39.1
SD	1.24
Birth weight (grams)	
M	3310
SD	414.54
Age at surgery (days)	
M	11.78
SD	6.75
Maternal level of education (%)*	
Low	3 (9.1)
Middle	13 (39.4)

High	16 (48.5)
Unknown	1 (3.0)
Genetic disorder (%)	3 (8.3)
24-month follow-up	
N	32
Male sex (%)	25 (78.1)
Age at follow-up (months)	24.3 (23.2-26.3)
5-year follow-up	
N	22
Male sex (%)	19 (86.4%)
Age at follow-up (years)	5.9 (5.5-6.7)

* As classified by the guidelines of Statistics Netherlands (Centraal Bureau voor de Statistiek [CBS]).

Measures

Cognition.

Bayley Scales for Infant and Toddler Development - Third Edition- NL [Bayley-III-NL]. The Bayley-III-NL (Van Baar, Steenis, Verhoeven, & Hessen), a translated and slightly adapted version of the original Bayley-III (Bayley, 2006), is a frequently used standardized instrument to assess development in infants and toddlers between 16 days and 42 months plus 15 days old. It consists of five developmental domains: Cognition, Language, Motor Function, Social-Emotional Function and Adaptive Behavior. The present study focuses on the Cognition Scale, which consists of 91 items and assesses general cognitive functioning on the basis of nonverbal activities involving memory, problem solving and manipulation. Raw scores were converted to standardized scores with a mean score of 100 and a standard deviation of 15. Reliability and construct validity of the Bayley-III-NL was rated by COTAN as 'sufficient' (Egberink, Janssen, & Vermeulen, 2006).

Wechsler Preschool and Primary Scale of Intelligence - Third Edition - NL

[WPPSI-III-NL]. At the age of five years, the WPPSI-III-NL (Wechsler, Hendriksen, & Hurks, 2006) was administered to assess intelligence. Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Symbol Search, Word Reasoning and Coding subtests were completed. Raw scores were converted into age appropriate normally distributed standardized scores (mean standard score 100, standard deviation 15) to derive Composite Verbal, Performance, Processing Speed and Full-Scale IQ scores [FSIQ]. COTAN rated reliability and criterion validity as 'sufficient' and construct validity as 'good' (Egberink, Janssen, & Vermeulen, 2010).

Behavior.

Child Behavior Checklist for ages 1½-5 [CBCL/1.5-5]. The CBCL/1.5-5 (Achenbach & Rescorla, 2000; Verhulst, Van der Ende, & Koot, 2000) is a questionnaire to obtain standardized parental or primary caregiver's reports on children's behavioral and emotional functioning. It consists of 99 questions about the behavior of the child in the last two months. The questions have to be answered on a 3-point scale, ranging from 'non-applicable' to 'clearly or often applicable'. The CBCL/1.5-5 consists of seven syndrome scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behavior (mean t-score 50, t-scores <65 normal range, t-scores 65-69 subclinical range, t-scores ≥70 clinical range). Furthermore, there are overarching scales for internalizing behavior (covering the first four syndrome scales), externalizing behavior (covering the last two syndrome scales) and total problem behavior (t-scores <60 normal range, t-scores 60-64 subclinical range, t-scores ≥ 65 clinical range).

Caregiver-Teacher Report Form for Ages 1½ - 5 [C-TRF]. The C-TRF is a questionnaire to assess emotional and behavioral functioning in young children according to the classroom teacher (Achenbach & Rescorla, 2000; Verhulst, Van der Ende, & Koot, 1997). It consists of 99 questions about the child's behavior that have to be answered on a 3-point scale. The C-TRF is subdivided in the six syndrome scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems and aggressive behavior (mean t-score 50, t-scores <65 normal range, t-scores 65-69 subclinical range, t-scores ≥70 clinical range). There are also overarching scales for internalizing behavior, externalizing behavior and total problem behavior (t-scores <60 normal range, t-scores 60-64 subclinical range, t-scores ≥ 65 clinical range).

Design and procedure

The present study had a longitudinal design and consisted of two measuring moments. At both 24 months and 5 years, patients visited the Wilhelmina Children's Hospital, where a Bayley-III-NL respectively a WPPSI-III-NL was performed. At 24 months, at least one parent or caregiver was present during the assessment. At five years, the child was alone with the researcher in the research area during the assessment. At both measuring moments, parents were asked to fill in a CBCL/1.5-5 questionnaire prior to the visit. Prior to the second measuring moment, the teachers of the children were asked to fill in a C-TRF questionnaire. All measures were performed by experienced clinicians or well-trained interns in the last year of their master's education. This follow-up study was approved by the Medical Ethical Committee of the UMCU. Written informed consent was provided by the parents of all included children.

Data analysis

IBM SPSS 22.0 was used to perform statistical analyses. One sample *t* tests were performed in the univariate analysis to determine whether the sample mean of cognition and behavior at 24 months and intelligence and behavior at 5 years of the CHD children differed from TD children.

A linear regression model was used to examine the predictive value of the score on the Bayley-III-NL Cognition Scale at 24 months for the score on the WPPSI-III-NL FSIQ scale at five years. Multiple regression models were used to examine the predictive value of attention problems according to parents on attention problems according to teachers, as well as the predictive value of attention problems at 24 months and five years on the score on the WPPSI-III-NL FSIQ and Processing Speed scales at five years.

Results

Cognition

24-month follow-up. A one sample *t* test revealed that mean cognition score at age 24 months (M = 102.44, SD = 17.01) was 2.44 points 95% CI [-3.69, 8,57] higher than the average cognition score of 100, but this was not statistically significant, t (31) = .81, p = .424. The Shapiro-Wilk statistic confirmed normal distribution of the Bayley-III-NL cognition scores.

Five-year follow-up. One sample *t* tests revealed that mean WPPSI-III-NL FSIQ score of the CHD group (M = 94.05, SD = 16.602) was almost 6 points below the average TD children's WPPSI-III-NL FSIQ score, but this difference wasn't found to be statistically significant. There were no statistically significant differences for VIQ and PIQ either. On the other hand, average

processing speed of the CHD children (M = 85.86, SD = 13.53) was almost 15 points lower than the average TD children's processing speed score. This difference was found to be statistically significant, and large, d = 1.05. The WPPSI-III-NL scores were approximately normally distributed. All results are presented in Table 2.

Table 2

Results one sample t tests WPPSI-III-NL

	t	df	Sig. (2-tailed)	Mean difference	95% CI	
					Lower	Upper
Full Scale IQ	-1.60	21	.124	-5.955	-13.68	1.77
Verbal IQ	-1.05	21	.304	-3.619	-10.78	3/54
Performance IQ	-.74	21	.467	-2.909	-11.07	5.26
Processing Speed	-4.90	21	<.001	-14.136	-20.13	-8.14

Behavior

24-month follow-up. One sample *t* tests, executed for every CBCL/1.5-5 syndrome scale and for the overarching internalizing, externalizing scales, indicate that the CHD children show statistically significant less anxious/depressed behavior and withdrawn/depressed behavior than do TD children. On the overarching externalizing, internalizing and total scales, no significant differences were found. Results are presented in Table 3.

Table 3

Results one sample t tests CBCL/1.5-5 24-month follow-up

	t	df	Sig. (2-tailed)	Mean difference	95% CI	
					Lower	Upper
Internalizing problems	-1.19	31	.25	-1.85	-5.03	1.33
Emotionally Reactive	-.79	31	.44	-.40	1.43	.63
Anxious/Depressed	-5.97	31	<.001	-1.81	-2.42	-1.19

Somatic Complaints	-2.05	31	.84	-.08	-.89	.73
Withdrawn/Depressed	-2.03	31	.05	-.66	-1.32	.00
Externalizing problems	-.07	31	.94	.13	-3.60	3.87
Attention Problems	1.37	31	.18	.63	-.31	1.56
Aggressive Behavior	-1.34	31	.19	-1.62	-4.08	.84

5-year follow-up. One sample *t* tests were used to compare the behavior, rated by parents and teacher, of the 5-year-old CHD children against TD children. Results indicate that, according to both their parents and teachers, CHD children show statistically significant less anxious/depressed behavior, with a large effect size for parents, $d = .81$, and a medium effect size for teachers, $d = .50$. Only teachers report statistically significant more attention problems in CHD children, with medium effect size $d = .56$. No differences were found in internalizing and externalizing behavior. All results are shown in Tables 4 and 5.

Table 4

Results one sample t tests CBCL/1.5-5, 5-year follow-up

	t	df	Sig. (2-tailed)	Mean difference	95% CI	
					Lower	Upper
Internalizing problems	-2.38	22	.81	-.34	-3.29	2.61
Emotionally Reactive	.753	22	.46	.47	-.82	1.76
Anxious/Depressed	-3.88	22	<.001	-1.12	-1.71	-.52
Somatic Complaints	.17	22	.87	.07	-.80	.94
Withdrawn/Depressed	.58	22	.57	.24	-.62	1.10
Externalizing problems	-.12	22	.91	-.20	-3.71	3.30
Attention Problems	1.44	22	.16	.85	-.37	2.07
Aggressive Behavior	-.82	22	.42	-1.05	-3.73	1.62

Table 5

Results one sample t tests C-TRF, 5 year follow-up

	t	df	Sig. (2-tailed)	Mean difference	95% CI	
					Lower	Upper
Internalizing problems	-2.19	21	.83	-.24	-2.48	2.01
Emotionally Reactive	.23	21	.82	.10	-.82	1.02
Anxious/Depressed	-2.32	21	.03	-.79	-1.49	-.08
Somatic Complaints	-1.34	21	.19	-.19	-.49	.10
Withdrawn/Depressed	.80	21	.43	.42	-.67	1.50
Externalizing problems	.68	21	.51	1.50	-3.12	6.11
Attention Problems	2.61	21	.02	2.59	.53	4.66
Aggressive Behavior	-.67	21	.51	.90	-3.69	1.89

Linear regression

Predictive ability Bayley-III-NL on WPPSI-III-NL. To predict the FSIQ score on the WPPSI-III-NL at 5 years old based on the composite score on the Bayley-III-NL Cognition Scale at 24 months old, a linear regression analysis was applied. All assumptions were met. Higher scores on the Bayley-III-NL composite cognitive scale at 24 months were associated with higher FSIQ scores on the WPPSI-III-NL at the age of five years: $R^2 = .577$, adjusted $R^2 = .554$, F (1,19) = 25.865, $p < .001$ (Figure 1).

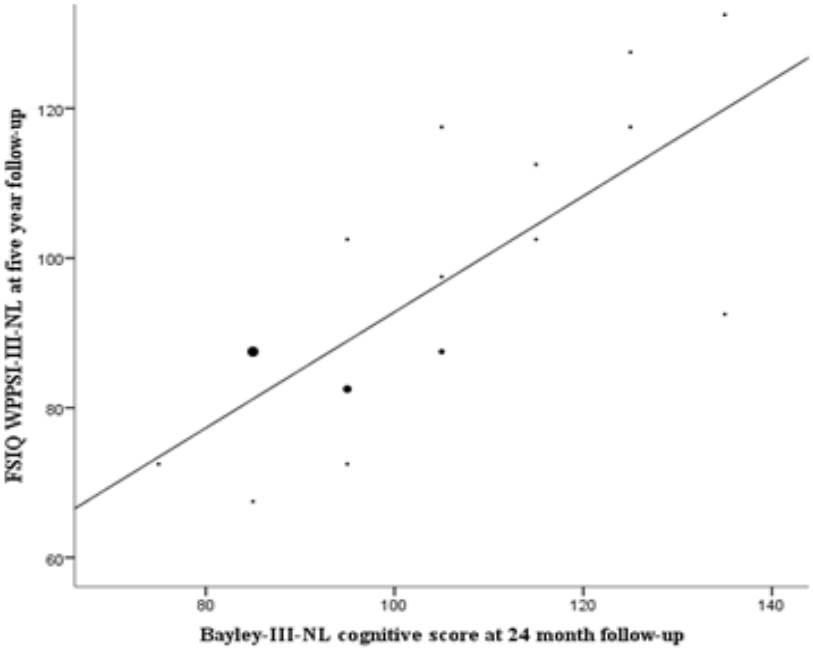

Figure 1.
Scatterplot of the Bayley-III-NL Cognitive Scale score at 24 months against WPPSI-III-NL FSIQ score at five years with fitted regression line.

Predictive ability attention according to parents on attention according to teachers. A multiple linear regression was applied to predict attention problem scores according to teachers at age five years (C-TRF) based on attention problem scores by parents at age 24 months and age five years (CBCL/1.5-5). All assumptions were met.

A statistically significant regression equation was found, $R^2 = .328$, adjusted $R^2 = .253$, $F = 4.383$, $p < .05$. Only the attention score by parents at age five years turned out to be a statistically significant predictor of attention problem scores reported by teachers. Higher attention problem scores according to parents at the age of five years were associated with higher attention problem scores according to teachers at the age of five years. Unstandardized (*B*) and standardized (β) regression coefficients and squared semi-partial correlations (sr^2) for each predictor in the regression model are reported in Table 6.

Table 6

Unstandardized (B) and standardized (β) regression coefficients and squared semi-partial correlations (sr^2) for each predictor in a regression model predicting C-TRF attention problem scores using CBCL/1.5-5 attention problem scores at 24 months and five years

Variable	*B* [95% CI]	β	sr^2
CBCL/1.5-5 24 months	-.408 [-.314-6.460]	-.185	.025
CBCL/1.5-5 5 years	1.172 [.313-2.032]*	.644	.307

Note. N = 21. CI = confidence interval

*$p < .05$

Predictive ability attention problems on intelligence. To estimate the proportion in variance in WPPSI-III-NL FSIQ scores that can be accounted for by the attention scores on the CBCL/1.5-5 and the C-TRF, a multiple regression analysis was performed. The assumption of normality was violated as there were a few outliers. Assumptions of normality, linearity and homoscedasticity of residuals, as well as multicollinearity were met.

In combination, the attention problem scores on the CBCL/1.5-5 at both 24 months and five years and the attention problem scores on the C-TRF accounted for 34.4% of the variability in FSIQ scores, $R^2 = .344$, adjusted $R^2 = .212$, F (3, 15) = 2.618, $p = .089$. Only the C-TRF attention problem score proved to be a statistically significant predictor of the FSIQ score. Higher C-TRF attention problem scores predicted lower FSIQ scores. Unstandardized (*B*) and standardized (β) regression coefficients and squared semi-partial correlations (sr^2) for each predictor in the regression model are reported in Table 7.

Table 7

Unstandardized (B) and standardized (β) regression coefficients and squared semi-partial correlations (sr^2) for each predictor in a regression model predicting FSIQ scores using attention problem scores at 24 months and five years

Variable	*B* [95% CI]	β	sr^2
CBCL/1.5-5 24 months	2.320 [-2.013-6.652]	.279	.057

CBCL/1.5-5 5 years	1.352 [-2.924-5.629]	.198	.002
C-TRF 5 years	-2.632 [-4.944-- .319] *	-.630	-.257

Note. $N = 19$. CI = confidence interval.

*$p < .05$.

Discussion

In the present longitudinal study, cognition and behavior in preschool and early childhood were examined in Dutch children who underwent neonatal cardiac surgery (in the period 2009-2012). Results show that the CHD children in the present study have cognitive abilities within the reference range. The mean score at age 24 months is practically equal to the population's mean score, while the mean score at age five is somewhat lower. Cognitive score at 24 months is nevertheless an important predictor of FSIQ score at age five. In terms of behavior, CHD children show at age 24 months less anxious/depressed and withdrawn/depressed behavior and less anxious/depressed behavior at age five. Teachers report more attention problems at age five, unlike parents. Attention problem scores of parents nevertheless predict attention problems scores of teachers. Moreover, attention problems reported by teachers are an important predictor of FSIQ at age five.

The lower but in reference range FSIQ score corresponds to earlier research, in which the children also generally score in the average range, but lower than the population's average (Griffin et al., 2003; Majnemer et al., 2008; Uzark et al., 1998), but contradicts other research, in which CHD children were found to score below the normal range (Creighton et al., 2007; Kern, Hinton, Nereo, Hayes, & Gersony, 1998; Mahle et al., 2005).

When interpreting the results of the full-scale intelligence scores, it is important to consider that the processing speed score has influence on this score, as one of the processing speed tasks is included in the calculation of the FSIQ. In contrast to full-scale intelligence scores, the children in the current study score significantly lower at processing speed than do their typically developing peers, with the sample's mean score about one standard deviation below the average. Little research has been done before into processing speed in children with CHD. Wray and Sensky (2001) found that only children suffering a cyanotic heart disease, in which a circulatory or ventilatory problem leads to poor blood oxygenation in the lungs, had processing

speed problems. The heart diseases represented in the present study are among these so-called cyanotic heart defects, so the results correspond to the findings of Wray and Sensky (2001).

With regard to cognition at longer term, the Bayley-III-NL Cognition scores take charge of a fair amount of the prediction of the WPPSI-III-NL FSIQ scores. It is notable though that the average WPPSI-III-NL FSIQ score is considerably lower than the Bayley-III-NL Cognition score, while for both measures the average score is 100. This contradicts the findings of Creighton et al. (2007), that suggest an upward trend from two years to five years, as well as the findings of Karsdorp and colleagues (2007), which state that cognition remains relatively stable across the years. Actually, the Bayley-III-NL is a measure that focuses on development rather than on intelligence, so the constructs of the two instruments differ from one another, which can explain the difference. Acton and colleagues (2011) suggest that the Bayley-III Cognition Scale might overestimate the development of children who underwent cardiac surgery by ten points, compared to a previous edition of the Bayley scales. The study by Acton et al. (2011) however used the American version of the Bayley-III. It is not known whether this also applies to the Dutch version.

Striking and in contrast with earlier research, is the fact that parents as well as teachers, did not report more internalizing problems in these children and even less anxious/depressed behavior. This is inconsistent with the majority of earlier studies (Hövels-Gürich et al., 2002; Majnemer et al, 2008; Miatton et al., 2007b). This applies particular to the study of Hövels-Gürich et al. (2002), according to which children with CHD show more anxious/depressed behavior than a healthy control group, although the children in that study were somewhat older. It is hard to explain why the children in the present study do not show these problems. Other studies explain the internalizing problems as a result of frequent hospital visits and restrictions in daily life such as social activities (Miatton et al., 2007b). It is possible that the children in the present study do not (yet) experience limitations in daily life. Another explanation might be that parents have different expectations of their children due to their disease, causing them to not experience anxious/depressed behavior as a problem.

The outcome of the present study with respect to attention problems is partly in line with previous findings, as only teachers report more attention problems in these children. In a study by Schillingford and colleagues (2008), it was, on the contrary, the parents who reported more attention problems. Teachers however have more experience when it comes to knowledge of

what is normal in child development and have the opportunity to compare the children in the classroom, what may help to differentiate between normal and deviant behavior (Grietens et al., 2004).

New in the field of congenital heart disease, is that attention, in particular reported by the teacher, is a predictor of intelligence. Literature does not unanimous reflect on whether attention on itself predicts intelligence, or that the relationship is due to some other underlying factor.. Earlier research however reported lower processing speed scores in children with attention problems, as processing speed tasks appeal to the sustainment of attention, which may be a problem for these children (Hurks, Hendriksen, Dek, & Kooij, 2010; Meyes & Calhoun, 2006). A possible explanation is that the processing speed task of the WPPSI-III-NL acts as a mediator in the relation between attention and full-scale intelligence scores, but more research is needed to sort this out.

Limitations and clinical implications. A limitation of the present study is that children with coactions or interruption of the aortic arch with as well as without hypoplastic left heart syndrome were enrolled. Children with HLHS have a more severe medical condition than children with only a coarctation or interruption of the aortic arch as they require staged surgical reconstruction and therefore more surgeries. A number of studies indicate lower cognitive scores for children with HLHS compared to children with other heart diseases (Creighton et al., 2007; Goldberg et al., 2000; Miatton et al., 2007a). This may also apply for behavior, as Brosig and colleagues (2007) found out that children with HLHS have more (externalizing) problems compared to children with other heart diseases. A second limitation is that some children that participated at 24 months didn't (fully) participate at age five, for a variety of reasons. This primarily influences the number of participants, but could also have its effects on the results.

For the clinical value of the present study, it is very important to mention that although it may seem that there are few participants, these are all (surviving) patients born with a coarctation or interruption of the aortic arch in the Netherlands between 2009 and 2012. In other words, at the first look, the number of participants may appear to be a limitation of this study, but fortunately, relatively few children are born with this kind of cardiac disease. The Wilhelmina Children's Hospital is the nationwide center in the Netherlands to which children diagnosed with coarctation or interruption of the aortic arch are transferred. Despite the high clinical value of the present study, it is desirable that more studies focus on the longitudinal effects of (neonatal

surgery on) children with a congenital heart disease on cognition and behavior. Especially the relation between attention and cognition has to be further investigated to confirm the findings of the present study.

It is important to keep following the children from the present study for a longer period. The present study gives an impression of the development in the preschool and early childhood age, which means that most of the children are only attending kindergarten at the second measuring moment. The transition to grade one and the further course of primary school will give more insight in the development of cognition, as intelligence is a more stable construct from an age of approximately eight years (Resing & Drenth, 2007) and academic attainment depends on more than intelligence. Although the present study indicates a problem in the processing speed of these children, it is difficult to reliably determine processing speed at age five. Reassessing processing speed at a later age can provide a more reliable representation. Furthermore, following these children will give the opportunity to examine executive functioning, as this may also be affected after neonatal surgery for congenital heart disease (Latal, 2016). According to Friedman and colleagues (2007), executive function might also be predicted by teacher-rated attention problems, so this gives implications for future research as well.

In summary, the children in this cohort are developing relatively well with intelligence in the reference range and few internalizing problems. Processing speed and teacher-reported attention are two things to take into account, as the processing speed is explicitly lower and teachers report more attention problems. The present study adds a new angle to the research on congenital heart disease in children by connecting behavioral outcomes to cognitive outcomes, as teacher-reported attention predict full-scale intelligence and processing speed.

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