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Cognitive Function in Pediatric Hypoplastic Left Heart Syndrome: Systematic Review and Meta-Analysis

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Abstract

Objective   Despite surgical palliation, children with hypoplastic left heart syndrome (HLHS) have compromised cardiac functioning and increased risk for cognitive deficits. We quantitatively reviewed the empirical data from this literature. **Methods**   The present meta-analysis included 13 studies reporting cognitive function for children with HLHS between the ages of 2 years and 6 months and 17 years that used standardized assessments of Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ). Differences in cognitive function were assessed relative to normative data, and we examined sample mean age and publication year as moderators. **Results**   Large effects were found for FSIQ ($g = -.87$, 95% CI [-1.10, $-.65$], $M = 86.88$) and PIQ ($g = -.89$, 95% CI [-1.11, $-.68$], $M = 86.56$), and a medium effect was found for VIQ ($g = -.61$, 95% CI [$-.84$, $-.38$], $M = 90.82$). All models demonstrated significant heterogeneity. Meta-regression analyses of effect size via Hedges' g on child age revealed a significant effect on FSIQ (coefficient $= -.07$, 95% CI [$-.12$, $-.01$], $p < .01$, $R^2 = .40$) indicating a loss of 1.1 FSIQ points across studies with each increased year of mean sample age. **Conclusions**   Deficits in FSIQ may reflect chronic brain injury or failure to make expected gains as children age. This review highlights the importance of early intervention in this population, and the need for longitudinal studies analyzing more specific domains of cognitive function and potential moderators.

Key words: age; cognitive deficit; congenital heart disease; HLHS; meta-analysis.

Introduction

Hypoplastic left heart syndrome (HLHS) is a congenital heart defect characterized by impairment in the development of the left side of the heart, including the mitral valves, aortic valve, and aorta. Consequently, infants with HLHS are unable to pump oxygen-rich blood through the body. Standard of care primarily includes a series of palliative surgical interventions beginning in the newborn period and extending through early childhood (Norwood procedure, bidirectional Glenn procedure, followed by the Fontan procedure) to increase blood flow and bypass the underdeveloped left side of the heart, allowing the right ventricle to become the main pumping chamber to the body (Feinstein et al., 2012). While congenital heart disease (CHD) is the most common congenital disorder and is identified in 1% newborns, HLHS is arguably the most severe form of CHD (Canfield et al., 2006).

Prior to the advent of modern surgical techniques HLHS was universally fatal.

Due to these surgical procedures, life expectancy has significantly increased with 10-year survival reaching 89% (d'Udekem et al., 2014), leading to increased attention on survivors. Despite improvements in procedural techniques for HLHS repair, children continue to have compromised postoperative systemic cardiac output, reduced systemic oxygen delivery, high systemic oxygen extraction, and anaerobic end-organ dysfunction (Feinstein et al., 2012). Children with HLHS have more surgeries, cardiac catheterizations, and hospitalizations compared with children with other complex congenital heart lesions and have been identified as being at the highest risk for developmental disability (Gerstle, Beebe, Drotar, Cassedy, & Marino, 2016; Marino et al., 2012). Reductions in social competence, communication, and adaptive behavior have also been noted (Ikle, Hale, Fashaw, Boucek, & Rosenberg, 2003). As the number of children surviving with HLHS has increased, tracking their long-term function has become increasingly important.

One of the primary long-term consequences of HLHS is impaired cognitive development and brain function. HLHS and other types of CHD are associated with increased risk for neurodevelopmental disabilities (Mahle & Wernovsky, 2001; Marelli, Miller, Marino, Jefferson, & Newburger, 2016). Two meta-analytic reviews have summarized findings on cognitive deficits in children with HLHS from infancy through 12 years of age. First, in a meta-analysis of cognitive function in children and adolescents with several types of CHD, Karsdorp, Everaerd, Kindt, and Mulder (2007) analyzed four studies reporting Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) published up to 2005. Results showed large deficits in FSIQ and PIQ, and medium deficits in VIQ for children with HLHS. Children with other forms of CHD showed negligible to small deficits in FSIQ, VIQ, and PIQ. This finding implies that the long-term cognitive effects of HLHS may be greater than those of other forms of CHD. Sistino and Bonilha (2012) reported secondary analyses of IQ as a part of a larger quantitative review reporting changes in hospital survival in preschool and school-aged children with HLHS using 10 studies published up to 2010. Preschool children with HLHS scored in the low average range on the Bayley II Mental Development Index. They also examined FSIQ, assessed by standardized measures of intelligence in school-aged children (ages 6–12 years), and the mean FSIQ of children with HLHS was in the low average range.

Findings reported by Karsdorp et al. (2007) and Sistino and Bonilha (2012) highlight the importance of further investigation of cognitive function for children with HLHS and provide a baseline for the field;

however, these reviews had several limitations. First, Karsdorp et al. (2007) only included four studies of children with HLHS available at that time, with a mean sample age ranging from 2.8 to 9.0 years. Sistino and Bonilha reported mean FSIQ across studies for school-aged children, but not standardized effect sizes for functioning in both preschool and school-aged children. Finally, neither of the previous reviews assessed moderators of effect sizes. Due to evidence of the cumulative and synergistic nature of risk factors associated with CHD throughout development (Marelli et al., 2016), child age may be related to increased deficits in functioning. Children with CHD are living through adolescence and early adulthood (d'Udekem et al., 2014); the inclusion of adolescents is imperative to understanding the long-term impact of HLHS on cognition. Further, as medical protocols and interventions improve over time, study publication year may also be an important moderator of effects.

A quantitative review of the current research on cognitive function in children with HLHS can help to identify gaps in the literature and establish directions for future research, practice, and intervention. The goal of the present meta-analysis is to provide an updated quantitative review of all literature reporting cognitive function in children with HLHS, utilizing standardized tests of broad indices of cognitive function, including FSIQ, VIQ, and PIQ in order to replicate and extend findings from previous meta-analyses. We aimed to (a) determine levels of FSIQ, VIQ, and PIQ relative to the normative mean in children and adolescents with HLHS; and (b) determine if child age and study publication year act as linear moderators of these deficits.

Methods

Literature Search and Inclusion Criteria

We searched for original empirical studies to identify articles that examined cognitive functioning in children and adolescents with HLHS up to February 1, 2019 with no lower bound date in order to maximize available data. Our systematic literature search was conducted using PubMed and PsycINFO, with three specific sets of search terms. The first was (*cognition OR cognitive function OR intelligence*) AND (*hypoplastic left heart syndrome OR HLHS*) across all fields (i.e., title, abstract, keywords); the second was (*neurocognitive OR cognitive function OR cognitive impairment OR intellectual impairment OR cognitive deficit OR executive function*) AND (*hypoplastic left heart syndrome OR HLHS*); and the third was (*neurodevelopmental OR neuropsychological*) AND (*hypoplastic left heart syndrome OR HLHS*). We supplemented PubMed and PsycINFO searches using backward

searches reviewing the reference sections of published meta-analyses including HLHS and cognitive function. Studies were included if they contained original empirical data on cognitive function reporting (a) standardized Wechsler measures of intelligence (e.g., WPPSI or WISC or WASI); (b) data on children between 2 years and 6 months and 17 years of age; (c) data for a sample of children with HLHS.

Data Coding
The following information was extracted from each study where available: (a) measures of cognitive function; (b) sample size; (c) sample mean age; (d) publication year; and (e) summary statistics for the calculation of effect sizes. All studies were independently coded by two raters and discrepancies were resolved through discussion. Inter-rater reliability was .98. Cognitive function scores were categorized into (a) FSIQ, (b) VIQ, and (c) PIQ. One study (Oberhuber et al., 2017) reported more specific Wechsler scale composite scores. In this case, the Verbal Comprehension Index and Working Memory Index were coded into VIQ, and the Perceptual Reasoning Index and Processing Speed Index were coded into PIQ. Each index score was entered into the Comprehensive Meta-Analysis program (Version 3; Borenstein, Hedges, Higgins, & Rothstein, 2013), and data were collapsed within the program by using mean of the selected outcome and study as the unit of analysis. For studies providing only the median and confidence intervals for the data, the mean and standard deviation were calculated (Hozo et al., 2005). We used Cohen's (1988) guidelines for effect size interpretation.

Study Quality
Criteria from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute [NHLBI], 2014) were adapted for the current review, excluding items that were irrelevant to or inconsistent with the study aims and inclusion/exclusion criteria. Studies were assigned one point per each criterion met, which were summed for a total quality score of 0–7 (0 indicating lowest quality and 7 highest quality).

Statistical Approach
All analyses were conducted with the Comprehensive Meta-Analysis program (Version 3; Borenstein et al., 2013), using random effects models, as the studies varied in methodology and design; study as the unit of analysis; mean of the selected outcome measure for effect sizes; and subgroup within study as the unit of analysis for age analyses in order to capture all studies reporting any HLHS subgroups. For each cognitive domain, standardized weighted mean effect sizes (g), which correct for biases associated with small sample sizes, 95% confidence intervals, and an estimated heterogeneity statistic (Q) were calculated using the procedure of Hedges and Olkin (1985). The 95% confidence intervals of the weighted mean effect sizes represent the range in which the mean effect size will be in 95% of cases. Mean effects are considered significant if the confidence interval does not include zero. To analyze effects of continuous moderator variables, we conducted simple meta-regression analyses using mixed effects models.

Publication Bias
Systematic bias can lead to inflated estimates of effect sizes and incorrect conclusions as a result of selective publication for result direction or size. To assess for possible publication bias, we examined funnel plots, calculated Egger's tests to detect funnel plot asymmetry, and performed trim and fill analyses indicating how many studies would need to be included to achieve funnel plot symmetry (Egger et al., 1997; Duval & Tweedie, 2000).

Results

Study Characteristics
A total of 118 studies were screened for eligibility. Seventy-three studies did not report Wechsler measures of cognitive function, one reported one individual Wechsler subtest, and 11 did not report outcomes specific to an HLHS group (see Supplementary Figure 1 for a PRISMA diagram). Thirteen studies met our specified inclusion criteria ($N = 358$). The mean age across studies was 6.95 years. Thirteen reported FSIQ and 10 reported VIQ and PIQ. Descriptive statistics of each study and individual effect sizes can be found in Table I.

Effect Sizes
Scores on measures of cognitive function in samples of children and adolescents with HLHS were significantly lower than the normative mean across all domains (Table II). Findings showed large deficits in FSIQ, $g = -.87$, 95% CI [−1.10, −.65]. The mean FSIQ was 86.88 across studies and ranged from 70.40 to 94.90 (Figure 1). There was a medium effect for deficits in VIQ, $g = -.61$, 95% CI [−.96, −.50], with an overall mean of 90.82 across studies, ranging from 81.32 to 98.90 (Figure 2). The largest deficit was seen in PIQ, $g = -.89$, 95% CI [−1.11, −.68]. The mean PIQ across studies was 86.56, ranging from 78.00 to 94.50 (Figure 3). All models had significant heterogeneity, indicating the presence of potential moderators (Table II).

Table I. Mean Standard Scores for IQ Testing and Differences Between Groups

Study (year)	Country	Study design	n	Mean age (years)	Female (%)	Race (% white)	Seizure Hx (%)	Cognitive measure	IQ-HLHS	Difference	Effect size (g)	Study quality
Creighton et al. (2007)	CA	C	14	5.00	31	80	–	FSIQ	85.00	–15.00	–1.00	5
								VIQ	–	–	–	
								PIQ	–	–	–	
Gardner (2004)	USA	C	31	6.35	41	–	7	FSIQ	79.42	–20.58	–1.36	6
								VIQ	81.32	–18.68	–1.24	
								PIQ	81.23	–18.77	–1.24	
Gaynor et al. (2010)	USA	C	67	4.00	40	73	–	FSIQ	94.90	–5.10	–0.34	5
								VIQ	–	–	–	
								PIQ	–	–	–	
Goldberg et al. (2000)	USA	C	26	4.00	33	–	10	FSIQ	93.80	–6.20	–0.41	6
								VIQ	98.90	–1.10	–0.07	
								PIQ	89.70	–10.30	–0.68	
Hansen et al. (2016)	DE	C	42	4.50	35	–	–	FSIQ	94.00	–6.00	–0.40	5
								VIQ	97.00	–3.00	–0.20	
								PIQ	93.00	–7.00	–0.47	
Ikle et al. (2003)	USA	C	13	5.20	19	–	–	FSIQ	88.54	–11.46	–0.76	5
								VIQ	90.54	–9.46	–0.63	
								PIQ	88.85	–11.15	–0.74	
Kern et al. (1998)	USA	C	12	4.40	43	–	14	FSIQ	80.67	–19.33	–1.29	5
								VIQ	86.83	–13.17	–0.88	
								PIQ	78.00	–22.00	–1.47	
Mahle et al. (2000)	USA	C	28	8.90	37	–	–	FSIQ	84.50	–15.50	–1.03	5
								VIQ	87.50	–12.50	–0.83	
								PIQ	82.25	–17.75	–1.18	
Mahle et al. (2006)	USA	C	47	12.50	32	88	23*	FSIQ	85.50	–14.50	–0.97	4
								VIQ	88.50	–11.50	–0.77	
								PIQ	84.50	–15.50	–1.03	
Oberhuber et al. (2017)	AT	C	43	10.30	35	–	5	FSIQ	84.50	–15.50	–1.02	6
								VIQ	92.90	–7.10	–0.47	
								PIQ	84.05	–15.95	–1.06	
Sarajuuri et al. (2007)	FI	C	7	5.98	–	–	–	FSIQ	86.70	–13.30	–0.89	4
								VIQ	89.90	–10.10	–0.67	
								PIQ	89.60	–10.40	–0.69	
Sarajuuri et al. (2012)	FI	C	23	5.15	–	–	26	FSIQ	90.25	–9.75	–0.65	5
								VIQ	92.75	–7.25	–0.48	
								PIQ	94.50	–5.50	–0.37	
Wernovsky et al. (2000)	USA	C	5	14.10	45	–	7*	FSIQ	71.00	–29.00	–1.93	6
								VIQ	–	–	–	
								PIQ	–	–	–	
Overall			358	6.95								

Note. AT = Austria; CA = Canada; DE = Germany; FI = Finland; USA = United States of America; C = cross-sectional; FSIQ = Full Scale IQ; HLHS = hypoplastic left heart syndrome; VIQ = Verbal IQ; PIQ = Performance IQ. Mean age = the mean sample age. Seizure Hx = seizure history. Difference is calculated from the normed IQ (M = 100). Study quality = total study quality rating ranging from 0 to 7. – = study did not report this measure. * = denotes that the seizure history value was for preoperative seizure history, whereas all others were postoperatively assessed.

Table II. *HLHS Meta-Analysis on Neurocognitive Deficits*

Level	k	g	95% CI	Q
Full Scale IQ	13	−0.87***	−1.10 to −0.65	48.56***
Adjusted value		−0.73***	−0.96 to −0.50	73.27***
Verbal IQ	10	−0.61***	−0.84 to −0.38	30.11***
Performance IQ	10	−0.89***	−1.11 to −0.68	26.27**

Note. HLHS = hypoplastic left heart syndrome; k = number of studies included; g = mean effect size (Hedges' g); Q = estimated heterogeneity statistic. Adjusted values are shown for any effect size in which trim and fill analyses indicated publication bias.
$^*p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Moderator Analyses

Meta-regression analyses of Hedges' g on child age revealed a significant effect for FSIQ, coefficient = −0.07, 95% CI [−0.12, −0.01], $p < .05$, $R^2 = .40$, indicating that every year of increased age corresponds to a loss of 1.1 FSIQ points (Table III; Figure 4). There were no significant methodological moderators of FSIQ; total number of subtests in the FSIQ measure ($p = .27$), number of working memory subtests ($p = .32$), and number of processing speed subtests ($p = .24$) were all non-significant. Child age was not

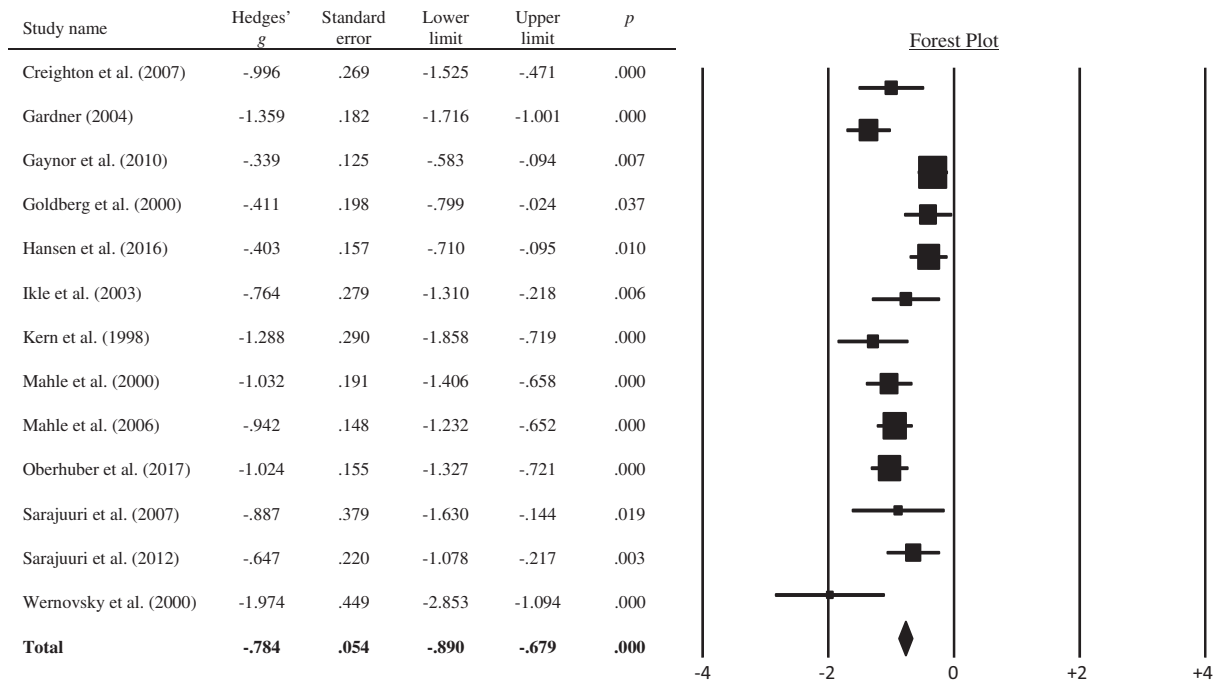| Study name	Hedges' g	Standard error	Lower limit	Upper limit	p	Forest Plot
Creighton et al. (2007)	-.996	.269	-1.525	-.471	.000	
Gardner (2004)	-1.359	.182	-1.716	-1.001	.000	
Gaynor et al. (2010)	-.339	.125	-.583	-.094	.007	
Goldberg et al. (2000)	-.411	.198	-.799	-.024	.037	
Hansen et al. (2016)	-.403	.157	-.710	-.095	.010	
Ikle et al. (2003)	-.764	.279	-1.310	-.218	.006	
Kern et al. (1998)	-1.288	.290	-1.858	-.719	.000	
Mahle et al. (2000)	-1.032	.191	-1.406	-.658	.000	
Mahle et al. (2006)	-.942	.148	-1.232	-.652	.000	
Oberhuber et al. (2017)	-1.024	.155	-1.327	-.721	.000	
Sarajuuri et al. (2007)	-.887	.379	-1.630	-.144	.019	
Sarajuuri et al. (2012)	-.647	.220	-1.078	-.217	.003	
Wernovsky et al. (2000)	-1.974	.449	-2.853	-1.094	.000	
Total	**-.784**	**.054**	**-.890**	**-.679**	**.000**	

Figure 1. Forest plot depicting results for Full Scale IQ in children with hypoplastic left heart syndrome relative to the normative mean. Hedges' g = estimate of effect size. Lower and upper limits reflect the 95% confidence intervals for the Hedges' g statistic.

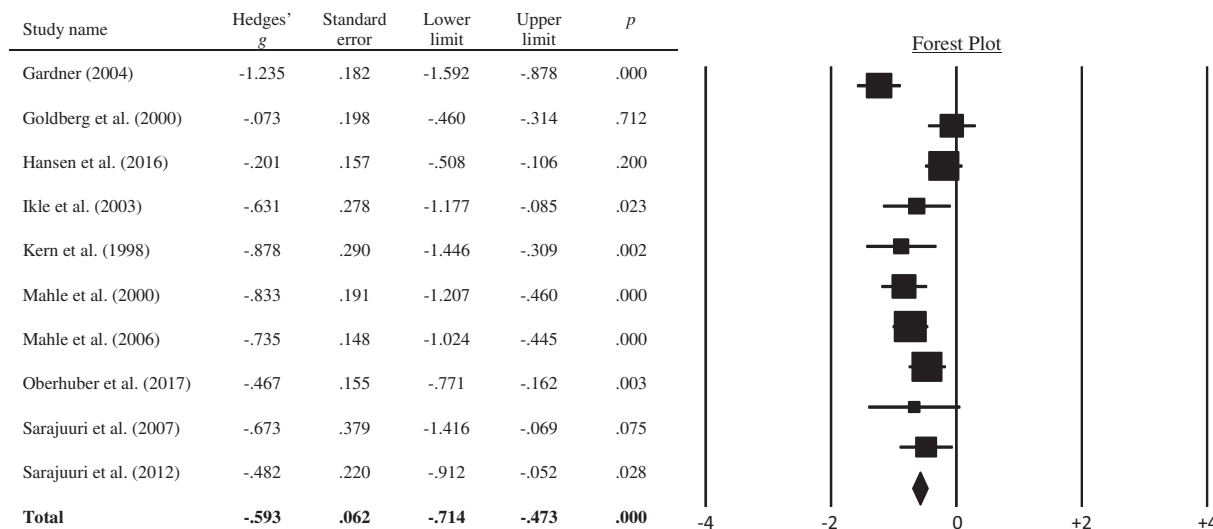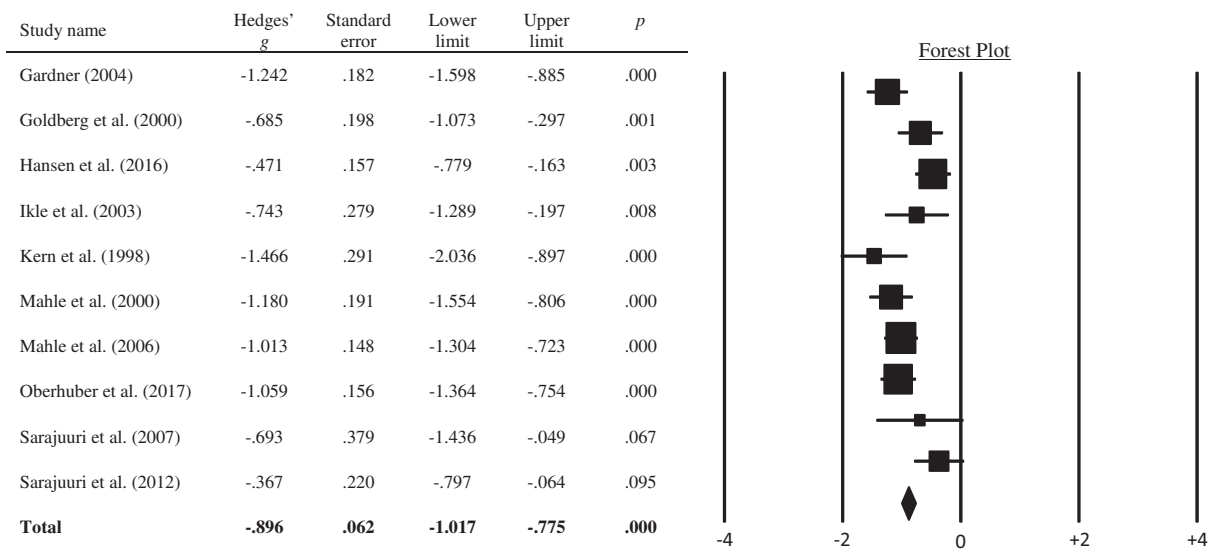| Study name	Hedges' g	Standard error	Lower limit	Upper limit	p	Forest Plot
Gardner (2004)	-1.235	.182	-1.592	-.878	.000	
Goldberg et al. (2000)	-.073	.198	-.460	-.314	.712	
Hansen et al. (2016)	-.201	.157	-.508	-.106	.200	
Ikle et al. (2003)	-.631	.278	-1.177	-.085	.023	
Kern et al. (1998)	-.878	.290	-1.446	-.309	.002	
Mahle et al. (2000)	-.833	.191	-1.207	-.460	.000	
Mahle et al. (2006)	-.735	.148	-1.024	-.445	.000	
Oberhuber et al. (2017)	-.467	.155	-.771	-.162	.003	
Sarajuuri et al. (2007)	-.673	.379	-1.416	-.069	.075	
Sarajuuri et al. (2012)	-.482	.220	-.912	-.052	.028	
Total	**-.593**	**.062**	**-.714**	**-.473**	**.000**	

Figure 2. Forest plot depicting results for Verbal IQ in children with hypoplastic left heart syndrome relative to the normative mean. Hedges' g = estimate of effect size. Lower and upper limits reflect the 95% confidence intervals for the Hedges' g statistic.

Study name	Hedges' g	Standard error	Lower limit	Upper limit	p	
Gardner (2004)	-1.242	.182	-1.598	-.885	.000	
Goldberg et al. (2000)	-.685	.198	-1.073	-.297	.001	
Hansen et al. (2016)	-.471	.157	-.779	-.163	.003	
Ikle et al. (2003)	-.743	.279	-1.289	-.197	.008	
Kern et al. (1998)	-1.466	.291	-2.036	-.897	.000	
Mahle et al. (2000)	-1.180	.191	-1.554	-.806	.000	
Mahle et al. (2006)	-1.013	.148	-1.304	-.723	.000	
Oberhuber et al. (2017)	-1.059	.156	-1.364	-.754	.000	
Sarajuuri et al. (2007)	-.693	.379	-1.436	-.049	.067	
Sarajuuri et al. (2012)	-.367	.220	-.797	-.064	.095	
Total	**-.896**	**.062**	**-1.017**	**-.775**	**.000**	

Figure 3. Forest plot depicting results for Performance IQ in children with hypoplastic left heart syndrome relative to the normative mean. Hedges' g = estimate of effect size. Lower and upper limits reflect the 95% confidence intervals for the Hedges' g statistic.

Table III. *Meta-Regression Analyses of Hedges' g on Child Age*

Covariate	Coefficient	SE	95% CI	Z	Total R^2
FSIQ					.40
Intercept	−0.38	0.23	−0.83 to 0.07	−1.65	
Child age	−0.07	0.03	−0.12 to −0.01	−2.30*	
VIQ					.00
Intercept	−0.37	0.31	−0.99 to 0.24	−1.19	
Child age	−0.03	0.04	−0.11 to 0.04	−0.85	
PIQ					.23
Intercept	−0.56	0.26	−1.07 to −0.05	−2.16*	
Child age	−0.05	0.03	−0.02 to 0.02	−1.42	

Note. FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; SE = standard error.
*$p < .05$ **$p < .01$ ***$p < .001$.

associated with VIQ ($p = .39$) or PIQ ($p = .16$). No significant effects were found in regression analyses of Hedges' g for study publication year: FSIQ ($p = .15$), VIQ ($p = .29$), or PIQ ($p = .13$).

Quality Assessment

Quality ratings are depicted in Table I and Supplementary Figure 2. Seven criteria were used and study quality ranged from 4 to 7 ($M = 5.46$, $SD = .21$). Overall, studies infrequently included sample size justification/power analyses and rarely reported whether outcome assessors were blinded to participant status/diagnosis. Study quality ratings were not related to effect sizes for FSIQ ($r = −.29$; $p = .34$), VIQ ($r = .11$, $p = .76$), or PIQ ($r = −.17$, $p = .65$).

Publication Bias

The effect size for FSIQ revealed a non-significant Egger's test (regression intercept = −2.91 95% CI [−6.40, 0.57]), VIQ was non-significant (regression intercept = −0.91, 95% CI [−6.35, 4.52]), and PIQ was also non-significant (regression intercept = 0.13, 95% CI [−5.00, 5.26]). The funnel plots for the effect sizes are presented in Supplementary Figure 3. Trim and fill analyses revealed that the effect size for FSIQ required three values to be added to create a symmetrical funnel plot. Notably, this result remained significant, and these adjusted values are presented in Table II. Taken together, there is no evidence for publication bias.

Discussion

The present meta-analysis of cognitive function in children and adolescents with HLHS builds on previous research by providing an update of the literature, including both children and adolescents, examining multiple domains of cognitive function (FSIQ, VIQ, PIQ), and assessing the moderating effect of age on cognition. Findings replicated and extended previous research in children with HLHS, showing medium to large deficits relative to the normative mean across cognitive domains, and significant heterogeneity in all models, indicating potential moderators. A novel finding revealed that child age was a significant linear moderator of FSIQ across studies, such that greater sample mean age was associated with larger deficits in mean scores.

Our results showed large deficits in FSIQ and PIQ, and medium deficits in VIQ. The relatively larger deficits for PIQ compared with VIQ may be understood within the framework of fluid and crystallized intelligence (Fry & Hale, 2000). Fluid intelligence, most closely aligned with PIQ, is not static, can be affected
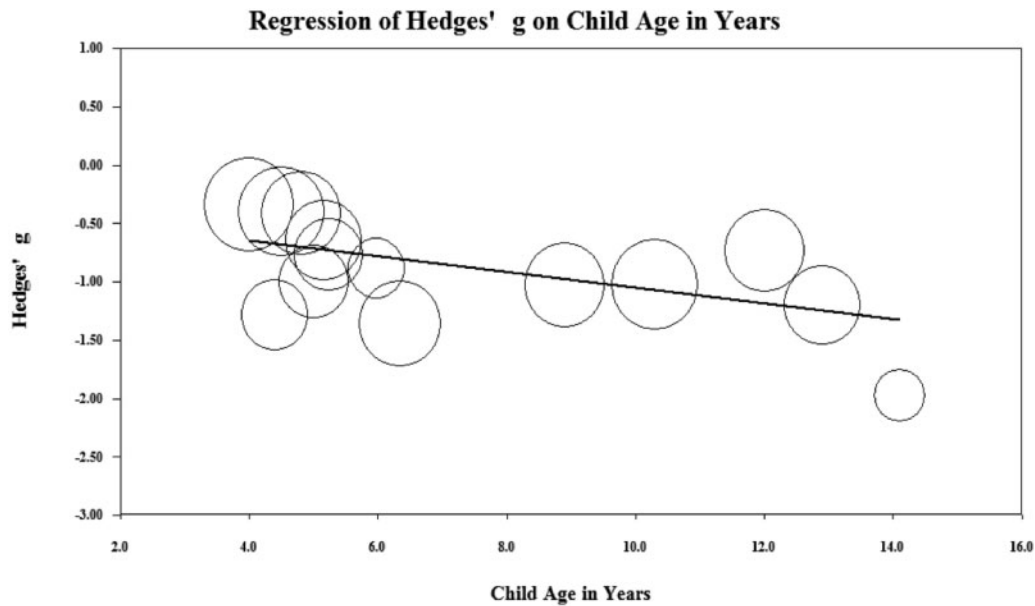
Figure 4. Scatter plot of meta-regression of Hedges' *g* for Full Scale IQ on child age. The *x*-axis reflects the mean child age in years for each study. The *y*-axis reflects the magnitude of the effect, indexed by Hedges' *g*.

by many maturational and experiential processes, and has been shown to be affected by intra- and perioperative factors in children with single ventricle defects, while crystalized intelligence was not (Vahsen, Bröder, Hraska, & Schneider, 2018). The pattern of effect sizes reported here include 13 studies of cognitive function in youth with HLHS and expand on findings from a previous meta-analysis of four studies from a decade prior (Karsdorp et al., 2007). This consistent pattern, in conjunction with non-significant effects for publication year in meta-regressions, indicates that these effects may be stable and highlights the potential need for additional assessment and services for children and adolescents with HLHS.

Significant heterogeneity in the effects found in the current meta-analysis could reflect the presence of moderators. There was significant heterogeneity in effects for VIQ, a composite of verbal comprehension and working memory, and PIQ, a composite of perceptual reasoning and processing speed, which may reflect variability among more specific cognitive functions. Previous research has been limited in that most studies have only examined overarching domains of cognitive function, while more specific domains are underutilized. Researchers are calling for complete evaluations on all domains of cognitive functioning in CHD as deficits in certain domains may support the presence of pathological substrates secondary to cardiac defects or surgery (Compas, Jaser, Reeslund, Patel, & Yarboi, 2017). Once a sufficient number of studies are available, assessing more specific domains of verbal comprehension, working memory, perceptual reasoning, and processing speed will be important

in future research in order to delineate profiles of deficits for targeted interventions.

Only one study to date reports more specific domains of cognitive function, with a sample of 43 children with HLHS. Oberhuber and colleagues (2017) report overall FSIQ in the low average range ($M = 84.5$, $SD = 20.8$), with scores ranging from 40 to 134. FSIQ was positively skewed, where more children scored in the below average range. There was a distinct pattern of individual index scores, with variability between verbal comprehension, perceptual reasoning, processing speed, and working memory. In addition to FSIQ, verbal comprehension ($M = 84.0$, $SD = 23.2$), perceptual reasoning ($M = 83.6$, $SD = 18.0$), and processing speed ($M = 84.5$, $SD = 18.0$) means were all in the low average range and positively skewed, with a larger proportion of children scoring in the lower ranges. Of note, working memory scores were in the average range ($M = 101.8$, $SD = 18.8$) and normally distributed. Alternatively, in a study of children aged 10–19 years with single ventricle lesions requiring the Fontan procedure (40% HLHS), children scored significantly lower on working memory ($M = 92.7$, $SD = 15.8$) than a referent group and the population mean (Bellinger et al., 2015). Future research should continue to utilize measures of specific domains of cognitive function in order to determine areas needing additional support.

Although emerging evidence suggests that children with all forms of CHD may be at risk for long-term neuropsychological consequences as they grow into adolescence and young adulthood (Marino et al., 2012), this is the first meta-analysis to show that age

is significantly related to child FSIQ in HLHS. Specifically, each year of increased mean sample age reflected a loss of 1.1 IQ points across studies, highlighting the importance of early intervention for children with HLHS, as cognitive deficits appear to be greater in older HLHS samples. It is important to note that our finding is limited as it is based on linear moderator analyses across studies, rather than within a cross-sectional sample or a longitudinal design.

There are three potential explanations for this finding. First, cognitive decline with age may reflect ongoing brain injury in children with HLHS, who are at high risk for stroke and with chronic hypoxia (Marelli et al., 2016; Watson, Stopp, Wypij, Newburger, & Rivkin, 2017). Second, without presuming further injury, cognitive function may worsen over time due to compromised integrative function during development. As cognitive and educational demands become more complex and abstract, children with HLHS may not be able to keep up with peers and make expected gains. Third, lower IQ among older children may be a result of cross-sectional study designs. For example, older child age may reflect older surgical and perfusion practices, resulting in potentially greater impact on cognition. In support of this idea, one study found that overall IQ in children with HLHS increased with year of surgery from 1989 to 1999 (Sistino & Bonilha, 2012). However, in the present analyses, year of surgery and operative information were not available, therefore we are unable to determine if younger children benefitted from improved techniques. Taken together, there is need for longitudinal studies, as well as research accounting for differences in treatment procedures within samples.

Marelli and colleagues (2016) argue that the opportunity for neurological injury and risk factors for negative developmental outcomes may be synergistic over time, with the brain at increased risk for vulnerability to injury. For those with CHD, the cumulative burden of reduced cardiovascular function in childhood and adolescence may lead to progressive cerebrovascular disease with age. Furthermore, children post-Fontan aged 10–19 years have been shown to have reduced brain volumes and cortical thickness compared with controls (Watson et al., 2017). The authors hypothesized that there may be greater regional reduction in gray matter volume among youth with Fontans due to hypoxia and relatively reduced cerebral perfusion characteristic of HLHS. In addition, white matter maturation is important for the development of cognitive functions (Nagy, Westerberg, & Klingberg, 2004). As compared with those without white matter injury, school-aged children with CHD and white matter injury have been shown to have lower FSIQ scores (Claessens et al., 2018). Similar results have been found in pediatric conditions, where decreased white matter maturation corresponded to lower cognitive function scores (e.g., premature birth, cancer survivorship) (Bells et al., 2017; Keunen et al., 2017). Other clinical populations have demonstrated a similar effect of decreased cognitive function in older children. For example, increased age has been shown to correspond to decreased FSIQ in children with sickle cell disease (Compas et al., 2017; King et al., 2014). Because both CHD and sickle cell disease are present from birth, child age also reflects illness duration. Therefore, accounting for age is important in the interpretation of these results, as cognitive deficits could reflect actual decreases in abilities or the failure to progress at the same rate as healthy peers.

With regard to heterogeneity due to other potential moderators, studies of children with single ventricle defects and Fontan procedure survivors report FSIQ scores ranging from low average to average, with some correlating with various factors including preoperative cerebral tissue oxygen saturation, birth weight, head circumference, age at surgery, postoperative length of stay, and seizure history (Gaynor et al., 2014; Goldberg et al., 2000; Hansen et al., 2016; Ikle et al., 2003; Kern, Hinton, Nereo, Hayes, & Gersony, 1998; Mahle et al., 2000, 2006; Oberhuber et al., 2017; Sarajuuri et al., 2012; Watson et al., 2017). It will be important for future research to explore correlates and potential factors contributing to variability in cognitive domains to better understand the effects of the disease and its treatment.

In light of research showing that working memory is affected by CHD (Bellinger et al., 2015), as well as risk of white matter injury affecting processing speed in this population, we analyzed the total number of subtests, and number of working memory and processing speed subtests as potential moderators. Since older children may be administered larger test batteries, they may appear to be performing worse than their younger counterparts as a function of the subtests included in analyses. None of the possible moderator effects were significant, suggesting that our findings were not due to the number of subtests included.

Studies of children with HLHS often do not account for comorbidities that may contribute to cognitive deficits. While some researchers note that results with exclusionary criteria are not generalizable to high-risk patients with HLHS, cognitive functioning cannot be attributed solely to an HLHS diagnosis (Mahle et al., 2006). In a sample of young children with HLHS, 25% had a genetic syndrome or abnormality, and these children were found to have lower mental development scores (Newburger et al., 2012). Future research should examine how these factors affect cognitive function in children with HLHS.

While we limited our search strategy to HLHS in an attempt to focus on a more homogeneous study population rather than including all children with single ventricle physiology who had undergone a Fontan procedure, it is important to note that children with other single ventricle lesions may have similar risks for cognitive deficits (Bellinger et al., 2015). Research also indicates that children with single ventricle defects, including HLHS, have higher rates of grade retention, more missed school days, and lower school competency, in addition to more surgeries, catheterizations, and fewer years since last hospitalization compared with those with two-ventricle lesions (Gerstle et al., 2016). In light of academic issues and barriers to academic engagement, following these children and adolescents into adulthood will be of utmost importance as cumulative disease burden may affect employment and quality of life. While research on adults with HLHS in particular is limited, adults with CHD report a higher prevalence of cognitive, physical, and activity limitations and decreased cognitive function compared with norms (Farr, Oster, Simeone, Gilboa, & Honein, 2016; Tyagi et al., 2014). The widespread and lifelong implications of HLHS call for interdisciplinary efforts involving physicians and psychologists to improve outcomes via closely monitoring risk for neurodevelopmental issues and employing early interventions to mitigate potential cognitive deficits for this population (Rappaport, 2015).

While contributing important findings to the literature, the present study highlights limitations that should be addressed in future empirical research. Research on HLHS across development has been sparse and includes small samples, therefore only 13 studies met inclusion criteria, all of which were cross-sectional ($N = 358$). The average age of all samples included in the present analyses was approximately 7 years old, and in light of age effects, the field would benefit from assessing cognitive function across development and into adulthood. In addition, we were only able to assess broad domains of cognitive function. Future research should employ full cognitive batteries, reporting more specific indices of cognitive function, since overall FSIQ may not reveal accurate cognitive profiles of youth with HLHS, nor be a true indicator of all skills. Study quality should also be considered when interpreting results from this systematic review. Quality assessment analyses highlighted limitations in the included studies. For example, only two studies specified whether assessors were blinded to participants' status/diagnosis or study objectives. And while most studies noted sample size as a limitation, few conducted a priori power analyses or reported effect sizes. This further underscores the need for meta-analyses to better understand cognitive functioning in HLHS survivors.

Future research should seek to determine factors contributing to more specific domains of cognitive function, including preoperative, operative, and postoperative factors, and other potential moderators. Intervention research would benefit this population by finding evidence-based methods for improving cognitive function. Finally, studies in CHD and other pediatric populations have shown that deficits in cognitive function are related to lower use of adaptive coping skills and increased internalizing symptoms (Prussien et al., 2018; Jackson, Gerardo, Monti, Schofield, & Vannatta, 2018). A previous meta-analysis found that in addition to cognitive deficits, children with CHD are at risk for psychosocial problems, including internalizing and externalizing behavior problems, especially in older children and adolescents (Karsdorp et al., 2007). This highlights the importance of delineating cognitive and psychosocial impairments in children with HLHS in order to provide adequate services and support.

Due to advances in surgical and medical care, survival for children with HLHS has increased dramatically, yet this population has been shown to have increased risk for cognitive deficits and lower quality of life compared with other chronic illnesses and complex congenital heart lesions (Gerstle et al., 2016; Marelli et al., 2016; Marino et al., 2012; Sistino & Bonilha, 2012). The present meta-analysis confirms and updates the current literature for FSIQ, VIQ, and PIQ and expands the review of cognitive function in children with HLHS to a wider age range. In addition, we found that measures of FSIQ, VIQ, and PIQ in children with HLHS are lower than norms, with medium and large effects, and have significant heterogeneity. Furthermore, increased child age predicted larger effects for deficits in FSIQ. These findings highlight the importance of further longitudinal research following children with HLHS through development tracking cognitive outcomes, and the need for early intervention to improve cognitive function and quality of life in this population.

Supplementary Data

Supplementary data can be found at: https://academic.oup.com/jpepsy.

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[An asterisk indicates studies included in meta-analysis]

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