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Cognitive and Attentional Function in Children with Hypoplastic Left Heart Syndrome: A Pilot Study

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Abstract

While survival for children with hypoplastic left heart syndrome (HLHS) has improved, compromised cardiac output and oxygen delivery persist, and children show cognitive deficits. Most research has assessed young children on broad cognitive indices; less is known about specific indices in older youth. In this pilot study, cognitive function and attention in youth ages 8 to 16 years with HLHS ($n = 20$) was assessed with the Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V) and NIH Toolbox Cognition Battery (NTCB); parents completed the Child Behavior Checklist. Children scored significantly lower than normative means on the WISC-V Full Scale IQ, Verbal Comprehension, Visual Spatial, Working Memory, and Processing Speed indices, and the NTCB Fluid Cognition Composite; effect sizes ranged from medium to large. Attention problems had a large significant effect. Child age corresponded to lower visual spatial scores. Findings highlight the importance of assessing multiple cognitive indices for targeted intervention and investigating age and disease factors as potential correlates in larger samples.

Keywords Congenital heart disease · HLHS · Cognition · Attention · Risk factors

The prevalence of congenital heart disease (CHD), particularly severe forms, has increased in children and adults in recent years due to improved diagnosis and advances in surgical techniques and postoperative management (Marelli et al., 2014). Hypoplastic left heart syndrome (HLHS) is a specific type of "single ventricle" congenital defect characterized by the inability to pump oxygen-rich blood to the body and is arguably the most severe form of CHD (Benjamin et al., 2018; Javed et al., 2019). Standard surgical techniques for HLHS palliation include three procedures (Norwood, Bi-Directional Glenn, and Fontan operations) to bypass the underdeveloped left side of the heart. Postoperatively, children continue to have compromised cardiac output, reduced systemic oxygen delivery, high systemic oxygen extraction, and anaerobic end-organ dysfunction (Benjamin et al., 2018; Feinstein et al., 2012). As 90% of children with HLHS now survive past infancy, the importance of tracking their outcomes into school-age years and beyond is amplified (Cassidy et al., 2018; Feinstein et al., 2012). However, questions remain regarding cognitive and behavioral functioning in this high-risk population.

A meta-analysis of cognitive function in adolescents and adults demonstrated inconsistent patterns of deficits when samples with all types of CHD were included (Mills, McCusker, Tennyson, & Hanna, 2018), not limited to HLHS. Children with CHD score lower than norms on Full Scale IQ and measures of verbal comprehension, perceptual reasoning, working memory, processing speed, and executive function, and for some abilities, the type of heart defect and cardiac procedure complexity correspond to even larger deficits (Cassidy, White, DeMaso, Newburger, & Bellinger, 2015; Gerstle, Beebe, Drotar, Cassedy, & Marino, 2016; Karsdorp, Everaerd, Kindt, & Mulder, 2007). Two meta-analyses of cognitive function found significant deficits in Full Scale IQ, Performance

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IQ, and Verbal IQ (Karsdorp et al., 2007; Siciliano et al., 2019). Prior research in children with HLHS has focused on these broad measures of cognitive function, with one exception (Oberhuber et al., 2017). Further research is needed to determine if cognitive impairment is sufficiently captured by broad measures or if children with HLHS perform differentially on more specific cognitive domains.

Children with CHD are also at greater risk for attention problems, as shown in a meta-analysis (Sterken, Lemiere, Vanhorebeek, Van den Berghe, & Mesotten, 2015). Similarly, the percentage of children with HLHS scoring in elevated ranges was about twice the typical rate in the average population (Brosig et al., 2013). Studies have found that inattention is the most commonly reported behavioral problem in children with HLHS and other single ventricle defects (Gaynor et al., 2014). In addition, adolescents with single ventricle physiology demonstrate an increased likelihood of attention-deficit/hyperactivity disorder (ADHD; DeMaso et al., 2017).

Children with single ventricle defects, particularly those who have undergone the Fontan palliation, are at high risk for adverse medical outcomes, low birth weight (LBW), and extended postoperative length of stay (LOS; Gaynor et al., 2014). Few studies have investigated the relation between LBW and LOS and cognitive and attentional function and have predominantly focused on children very early in development (Knirsch et al., 2012; Mahle et al., 2013; Newburger et al., 2012). In school-aged children, longer LOS has been related to lower VIQ, PIQ, and FSIQ (Mahle et al., 2006). In addition, children requiring mechanical support (e.g., extracorporeal membrane oxygenation and ventricular assist device) may be at risk for abnormal cognitive outcomes (Marino et al., 2012). Therefore, medical or disease factors that may contribute to variability in cognitive and attentional function deserve further investigation.

The aim of the current pilot study was to examine indices of cognitive function compared to national norms and the degree of attention problems in a sample of school-aged children and adolescents with HLHS. We utilized the Wechsler Intelligence Scales for Children – Fifth Edition (WISC-V) and the NIH Toolbox Cognition Battery (NTCB), a brief tool to assess cognitive function, which have yet to be used in this population. We hypothesized that children with HLHS would (1) demonstrate below average scores on all cognitive measures, (2) have increased attention problems, and these effects would be large. We expected that (3) poorer cognitive function would be related to more attention problems, and (4) that risk factors for poorer medical outcome (i.e., LBW, prolonged LOS, history of mechanical support) and older child age would be related to cognitive deficits and attention problems.

Materials and Method

Participants

Thirty-one children receiving medical care at our institution met inclusion criteria and were consecutively approached and invited to participate in the study. Inclusion criteria were (a) diagnosis of HLHS and completion of the Fontan palliation and (b) 8 to 16 years of age. Exclusion criteria were (a) DiGeorge Syndrome, Down Syndrome, or other suspected genetic syndromes; (b) neurological impairment that would prevent a child from utilizing computer-based cognitive programs; (c) prematurity with gestational age < 37 weeks; (d) epilepsy; and (e) non-English speaking. Out of 31 eligible patients approached, the 11 that declined participation did not differ from participants in age ($M = 10.58$, $p = .54$) or gender ($p = .19$). Reasons for declining included busy family schedules ($n = 2$), no interest in research ($n = 2$), inability to contact and schedule families ($n = 2$); five families did not indicate a reason. Twenty children and adolescents with HLHS were included in the final sample ($M_{years} = 11.20$, SD = 2.55); 80% were male, 90% were non-Hispanic white, and 10% were Hispanic.

Participant characteristics of the sample are presented in Table 1. All participants had an initial surgery during infancy. The median age at first cardiac surgery was four days (interquartile range 2.25 to 6.75 days). As defined by Marino and colleagues, nine participants had prolonged first surgery LOS (> 2 weeks) (Marino et al., 2012). The median number of cardiac surgeries prior to age five was three. Additional surgeries beyond the standard three surgeries for HLHS were to address postoperative complications (e.g., mediastinal fluid drainage, clot removal, pacemaker placement). Parental education varied; 10% of parents had a high school diploma or GED, 30% had some college, 25% had a college degree, 20% attended graduate or professional school, and 15% did not report their educational

Table 1 Participant demographic and medical characteristics

	Mean	SD	Range
Age (years)	11.20	2.55	8–16
Sex (*n* male)	16	–	–
Age at first cardiac surgery (days)	5.10	3.67	1.97–16.02
Cardiac surgeries before age 5[a]	3.00	.60	3–5
First surgery postoperative LOS (days)	77.51	85.30	12–328
Birth weight (kg)	3.30	.56	2.24–4.36
Hx of mechanical support or CPR (*n*)	7	–	–

$N = 20$ (full sample for all variables)

LOS length of stay, *Hx* history, *CPR* cardiopulmonary resuscitation

[a]Median shown for this variable

level. Family income ranged from less than $10,000 to over $80,000 annually, and the median income level category was $60,000-$70,000. Income information was declined or unavailable for three families. At the time of the study, 20% of participants were on medication for ADHD, 30% had repeated a grade in school, 45% had received special education services at some point, and 10% reported receiving special classroom accommodations (e.g., extra time, adjusted assignments and exams).

Measures

Cognitive Function

All participants completed the Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; Wechsler, 2014), a widely used and well-validated measure of cognitive function and intelligence. We examined Full Scale IQ (FSIQ), Verbal Comprehension Index (VCI), Visual Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI) and Processing Speed Index (PSI) for the current analyses. Participants also completed five subtests of the National Institutes of Health Toolbox Cognition Battery (NTCB), including the Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, Pattern Comparison Processing Speed Test, Picture Sequence Memory Test yielding a Fluid Cognition Composite, which was of particular interest, as it focuses on attention, memory, processing speed, and executive function. The NTCB is a standardized, computerized battery intended as a brief (30 min) and convenient neuropsychological battery for children with well-established validity and reliability (Bauer & Zelazo, 2013, 2014; Gershon et al., 2013). Scores for the WISC-V and NTCB are presented as standard scores ($M = 100$, $SD = 15$) based on age.

Child attention problems. Parents reported their child's school, social, and psychological functioning on the Child Behavior Checklist (CBCL). The Attention Problems subscale was Borderline scores range from T scores 65 to 69 (93rd–97th percentiles) and scores greater than 70 (≥ 98th percentile) are considered clinically significant. Reliability, validity, sensitivity, and specificity of the Attention Problems scale are well established (Achenbach & Rescorla, 2001; Chang, Wang, & Tsai, 2016).

Risk Factors

Risk factors for poor medical outcomes, including birth weight, postoperative LOS for first surgery, and history of mechanical circulatory support (extracorporeal membrane oxygenation or ventricular assist device use) were collected from medical charts and parental interview. Family income category (e.g., less than $10,000, $10,000–$20,000, $20,000–$30,000, $30,000–$40,000, $40,000–$50,000, $50,000–$60,000, $60,000–$70,000, $70,000–$80,000, and more than $80,000) was also included as a potential risk factor for poorer cognitive scores. History of mechanical support was rated as present or not present, while birth weight and LOS were treated as continuous variables.

Procedure

The study was approved by the Vanderbilt University Medical Center Institutional Review Board. Children were recruited from pediatric cardiology clinics at our institution in Nashville, Tennessee. Informed consent and assent were obtained from parents and children, respectively. Children and parents and children completed all study procedures in one lab visit. Measures were administered by doctoral and postdoctoral-level research assistants and supervised by a clinical psychologist. Participants were compensated for their time.

Statistical Power and Data Analyses

Statistical analyses were conducted with SPSS (version 25). Means, standard deviations, and one-sample t tests were computed to test hypotheses. We compared cognitive and attention problem scores to normative means using one-sample t tests. We assessed differences between children with and without a history of mechanical support using independent samples t tests. Bivariate Pearson correlations were used to assess associations between scores of cognitive function, attention problems, birth weight, and LOS. Correlations between the WISC-V and NTCB were included to determine the potential utility of the NTCB as a screening tool in clinical settings. Power analyses indicated that with $n = 20$, $\alpha = .05$, and power of .80, significant differences of medium-to-large effects could be detected for one-sample t tests ($d > .58$), independent t tests ($d > 1.21$), and correlations ($r > .50$). All tests were one-tailed, as we had specific directional hypotheses. We used Cohen's guidelines to interpret effect sizes (Cohen, 1988).

Results

Cognitive Function

Scores on performance measures cognitive function relative to the normative mean are presented in Table 2. FSIQ, VCI, VSI, and PSI scores on the WISC-V were significantly lower than normative means ($p < .05$), showing large effects, and were in the low average classification range (Table 2). The mean WMI score was also significantly lower than the

Table 2 Cognitive and attentional functioning

	Total sample			1.5 SD from mean (%)	Norm comparison	
	Mean	SD	Range		*t*	*d*
WISC-V[a]						
VCI	84.40	11.71	55–103	30	−5.96***	1.33
VSI	88.55	14.24	64–108	30	−3.60***	.80
FRI	94.80	14.39	67–112	25	−1.62^{+}	.36
WMI	93.65	13.89	62–115	15	−2.05*	.46
PSI	87.90	12.12	66–116	15	−4.46***	1.00
FSIQ	85.45	13.44	54–106	35	−4.84***	1.08
NTCB composite[a]	85.65	18.20	60–118	45	−3.53***	.79
CBCL attention[b]	60.11	7.62	50–83	15	5.78***	1.33

Cognitive outcomes and comparisons to normative samples including effect sizes. FRI remained nonsignificant and WMI was no longer significant after correcting for multiple comparisons; all other results remained

WISC-V Wechsler Intelligence Scale for Children – Fifth Edition, *VCI* Verbal Comprehension Index, *VSI* Visual Spatial Index, *FRI* Fluid Reasoning Index, *WMI* Working Memory Index, *PSI* Processing Speed Index, *FSIQ* Full Scale IQ, *NTCB Composite* NIH Toolbox Cognitive Battery Fluid Cognition Composite, *CBCL* Child Behavior Checklist Attention Problems, *SD* standard deviation; 1.5 SD from Mean = percentage of children scoring ± 1.5 SD from the mean. $N = 20$ for WISC-V and NTCB scores. $N = 19$ for CBCL scores

[a]WISC-V indices and NTCB composite scores are compared to standard scores: $M = 100$

[b]CBCL scores are compared to T-scores: $M = 50$

$^{+}p = .06$, * $p < .05$, *** $p < .001$

normative mean, approaching a medium effect, while the FRI was not statistically different from the standardization sample; the means on both of these scales were in the average range. NTCB Fluid Cognition Composite was significantly lower than the normative mean with a large effect. After correcting for seven comparisons across cognitive measures (Bonferroni; $p < .007$), all effects remained, with the exception of WMI, which was no longer significant.

Associations of NTCB and WISC-V

The NTCB Fluid Cognition Composite was significant related to the WISC-V FRI ($r = .46$, $p = .04$), WMI ($r = .78$, $p < .001$), PSI ($r = .48$, $p = .03$), and FSIQ ($r = .57$, $p = .008$), approached significance for the VCI ($r = .45$, $p = .05$), and did not significantly correlate with the VSI ($r = .24$, $p = .15$). Only the WMI and FSIQ remained significant after correcting for multiple comparisons (Bonferroni; $p < .008$).

Attention Problems

Parent report on the CBCL reflected significantly elevated scores on the Attention Problems scale, a large effect (Table 2). Five percent of parents rated their children as having elevated attention problems in the "clinical range" (≥ 98th percentile), and an additional 10% of parents rated their children has having attention problems in the "borderline clinical" range (93rd to 97th percentile) (Achenbach & Rescorla, 2001). Therefore, a total of 15% of our sample had elevated scores as compared to 7% of norms. No measures of cognitive function were significantly correlated with parent reported attention problems.

Risk Factor Analyses

There were no differences in cognitive function or attention problems as a function of history of mechanical support ($t < 1.73$). LOS was significantly skewed; two participants had extreme scores (> 2 SD) compared to the sample mean. When categorized as outliers and excluded from analysis, the data were no longer skewed ($M = 52.73$ days in the hospital, SD = 39.29, range 12–149). Longer postoperative LOS and LBW were not significantly related to cognitive or attention measures (both with the full sample and with outliers excluded), all small correlations. Family income did not significantly correlate with any cognitive or attention measures. Child age was not related to any risk factors.

Supplemental Analyses

Child age was negatively correlated with the VSI, $r = -.52$, $p = .02$, where older participants had lower VSI scores. No other cognitive scores were associated with age, and all correlations were small in magnitude. Independent samples *t* tests revealed that children receiving medication for ADHD ($n = 4$) scored higher on the CBCL Attention Problems scale

than children not on medication, but these two groups did not differ significantly on any of the cognitive measures. Children who had repeated a grade in school ($n=6$) scored significantly lower on the VCI, FRI, and FSIQ than those who had not been retained, and children who received special education services ($n=9$) scored significantly lower on the WMI, PSI, and FSIQ, and scored higher on the attention problems scale.

Discussion

The present pilot study provides an assessment of cognitive function and attention and is one of only a few studies in older children and adolescents with HLHS. The WISC-V and NTCB have not been previously tested in this population. Our preliminary results show significantly lower mean scores on nearly all cognitive measures compared to the normative mean and elevated attention problems. Children with HLHS had significantly poorer general intellectual functioning on the WISC-V FSIQ compared to healthy same-aged peers in the normative sample and scored significantly lower on the VCI, VSI, and PSI, all large effects. The WMI approached a medium effect, and there was a small effect for the FRI, though not significant. There were differences between cognitive indices, highlighting opportunities for targeted intervention in these children.

While meta-analyses of cognitive function have demonstrated that children with CHD and HLHS specifically score below their same-age peers on global cognitive measures, including Full Scale IQ, Verbal IQ, and Performance IQ (Karsdorp et al., 2007; Mills et al., 2018; Siciliano et al., 2019), only one other study to date reports more specific indices of cognitive function in children with HLHS (Oberhuber et al., 2017). This pilot study reported overall FSIQ in the low average range on the WISC-IV, with a distinct pattern of index scores: verbal comprehension, perceptual reasoning, and processing speed were in the low average range, and working memory was in the average range (Oberhuber et al., 2017). Another study of adolescents with single ventricle lesions (40% HLHS) found that children scored lower than norms on working memory tasks though still in the average range (Bellinger et al., 2015). Researchers have begun to investigate cognitive training programs targeting working memory in children with CHD and a pilot study has shown evidence for feasibility and short-term improvements on working memory tasks (Calderon et al., 2019; Jordan et al., 2019), yet examination of effect sizes suggests that working memory is not the greatest deficit for these children. Efforts to improve verbal comprehension, visuospatial skills, and processing speed may deserve equal attention for targeted interventions.

The current preliminary results showed no significant relations between cognitive scores and child age with the exception of visual spatial ability. VSI scores were negatively related to age, where older child age corresponded to poorer visual spatial scores. Some studies have reported visual spatial and visual motor deficits in children with HLHS (Brosig et al., 2013; Gaynor et al., 2014; Sarajuuri et al., 2007), while others have not (Brosig, Mussatto, Kuhn, & Tweddell, 2007), and none have reported differences with age. Larger deficits in FSIQ have been shown to be associated with age, highlighting the possibility that children with HLHS may experience ongoing brain injury with age or may plateau in cognitive ability in conjunction with increased cognitive demands, as older children with HLHS perform more poorly than healthy peers (Marelli, Miller, Marino, Jefferson, & Newburger, 2016; Siciliano et al., 2019; Watson, Stopp, Wypij, Newburger, & Rivkin, 2017). Older children and adolescents may experience increased cognitive, academic, and behavioral demands and expectations. Therefore, perhaps visual spatial abilities should be monitored as children with HLHS age, and the association between cognitive functioning and age should be explored in larger samples.

Exploratory correlational analyses revealed that birth weight and LOS were not related to cognitive measures, and there were no differences in cognitive function based on mechanical support history. In HLHS, postoperative LOS has been related to medical factors (Mosca et al., 2000), malnutrition (Kelleher, Laussen, Teixeira-Pinto, & Duggan, 2006), and/or lack of typical environmental inputs (e.g., school, communication) (Sananes et al., 2012), as well as decreased Verbal IQ (Mahle et al., 2006). Studies in children with CHD show that other physiological biomarkers are related to poorer cognitive outcomes (e.g., sleep-disordered breathing, lower arterial blood oxygen content, atrioventricular valve regurgitation; Wolfe et al., 2020), as well as mediate quality of life (Sanz et al., 2018). Medical factors should continue to be investigated, particularly those that are malleable, as they could indicate a greater need for monitoring cognitive functioning and obtaining cognitive testing for certain children.

Parent reported attention problems were significantly elevated compared to norms, with a large effect, consistent with previous research showing that children with complex CHD demonstrate more attention problems as measured by parent- and teacher-rated reports compared to other heart lesions (Brosig et al., 2007), normative samples (Brosig et al., 2013; Shillingford et al., 2008), and healthy sibling controls (Murphy et al., 2017), and are more likely to meet criteria for ADHD (DeMaso et al., 2017). It is important to note that the majority of research on attention in school-aged children has been measured via behavior rating scales versus objective measures (Cassidy et al., 2018). Contrary to hypotheses, parent reported attention problems were not

related to cognitive measures. Attention problems did not vary as a function of history of mechanical support and were unrelated to LOS and birth weight. No result for birth weight may reflect bias and range restriction in the current sample since children born premature were excluded, and those with low birth weights may be less likely to survive into middle childhood. Other reports of inattention and hyperactivity in children with complex cardiac lesions have shown no significant correlations between pre-, peri-, or postoperative variables (Shillingford et al., 2008). Children with HLHS may benefit from an increased emphasis on cognitive and behavioral interventions in order to bolster against the negative sequelae of disease, surgery, and perioperative complications.

Since youth with HLHS appear to demonstrate poorer cognitive outcomes compared to other CHD subtypes, it is important to identify measures that can be used reliably and cost-effectively in this high-risk population. A screening tool to identify children with HLHS who may require more comprehensive cognitive testing may be beneficial in light of insurance coverage and availability of academic testing, though comprehensive testing is often preferred (Cassidy et al., 2018). The NTCB is a brief neuropsychological assessment with good psychometric qualities, requires minimal training, can be administered in a hospital or outpatient setting, and is offered free of charge (Bauer & Zelazo, 2013; Gershon et al., 2013). The NTCB was not developed as a clinical measure to screen for impairment or substitute for full neuropsychological evaluation or diagnostic tool, but rather as a brief measure to supplement other outcomes measures in epidemiological or longitudinal research and clinical trials. While it's clinical utility is not yet fully understood, continued research with this measure with clinical populations, like the present study will expand its use, which could have clinical implications (Weintraub et al., 2013). The NTCB may be of particular interest to providers, as a full neuropsychological battery is a limited resource in many settings. Our preliminary results indicated that the NTCB may be a useful screen of cognitive function, as correlations with the VCI, FRI, WMI, PSI, and FSIQ ranged from medium to large in magnitude, though it corresponded significantly to only the WMI and FSIQ in this small sample. The NTCB may be a useful screening measure of cognitive abilities in children with HLHS yet future research with larger samples should test the sensitivity and specificity of this measure to determine how it compares to more comprehensive measures. In addition, while cognitive ability does not equate to school performance, below average scores may indicate a need for additional supports in academic spheres. Despite the high prevalence of impairment, a recent study showed that the majority of families of young children with HLHS are not accessing early interventions (Mussatto et al., 2018). Similar to children with other chronic health conditions, thorough cognitive testing for children with HLHS may be an invaluable avenue to identify those in need of classroom modifications and additional services (Compas, Jaser, Reeslund, Patel, & Yarboi, 2017).

The present pilot study has important limitations. Statistical power was limited by sample size. We were underpowered to detect small correlations or group differences. Larger multi-center samples are vital to determine factors (e.g., demographic, preoperative, perioperative, and postoperative) contributing to cognitive function. In small samples, sampling bias is possible. Demographic information was unavailable for the families who declined study participation, potentially limiting generalizability. The present sample differed from other studies in terms of WMI, and future work should report grade retention rates and reasons for grade retention in this population. While we focused on a homogeneous sample of children with HLHS, it is important to note that those with other single ventricle lesions are also at high risk for cognitive impairment (Bellinger et al., 2015). In addition, though HLHS occurs more often in males (55% to 70%) and other studies report high percentages of males (Bellinger et al., 2015; Chang, Chen, & Klitzner, 2002; Cleveland Clinic, n.d.; Yoo, 2018), our results may be less generalizable to the larger HLHS population, as our sample was predominantly male and White, reflective of the state demographics where the study was conducted.

In conclusion, the current pilot study reports on cognitive functioning, measured by the WISC-V and NTCB, which have not been tested previously in this population, and attentional problems in a sample of older children and adolescents with HLHS. The present study extends findings on overarching measures (e.g., Full Scale IQ, Verbal IQ, and Performance IQ) with an updated assessment of multiple indices of cognitive function, where large deficits were found on the majority of cognitive indices. Participants also demonstrated increased attention problems compared to norms. These difficulties could all considerably affect school and employment outcomes. Future research should build on these preliminary results to ascertain factors contributing to cognitive performance. This could allow clinicians to pinpoint specific areas of dysfunction in order to adequately provide targeted services and support for children with HLHS and their families, including early intervention and monitoring throughout development.

Author Contributions Study Conceptualization: LCJ, LKM, BEC; Methodology: LCJ, LKM, BEC; Formal analysis and investigation: RES, LKM, KVP, LMH, NJP, CAL; CMM, BEC, LCJ; Writing: RES, LWM, BEC, LCJ; Funding acquisition: LCJ, BEC, KVP; Resources: LCJ; Supervision: LCJ, BEC.

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Compliance with Ethical Standards

Conflict of interest Rachel E. Siciliano, Lexa K. Murphy, Kemar V. Prussien, Lauren M. Henry, Kelly H. Watson, Niral J. Patel, Chelsea A. Lee, Colleen M. McNally, Larry W. Markham, Bruce E. Compas, and Lori C. Jordan declare that they have no conflict of interest.

Ethical Approval All procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the 1964 Helsinki Declaration and its later amendments and has been approved by the institutional review board of Vanderbilt University Medical Center.

Informed Consent All parents and children completed informed consent and assent, respectively.

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