





ORIGINAL RESEARCH

Association Between Sleep Disturbances With Neurodevelopmental Problems and Decreased Health-Related Quality of Life in Children With Fontan Circulation

Kirstin Knobbe, MD; Meghana Partha , BS; Michael D. Seckeler , MD; Scott Klewer , MD; Chiu-Hsieh Hsu, PhD; Jamie Edgin, PhD; Wayne J. Morgan, MD; Natalie Provencio-Dean, MS; Silvia Lopez, RN; Sairam Parthasarathy, MD; Daniel Combs , MD

BACKGROUND: Children with Fontan circulation are known to be at increased risk for neurodevelopmental problems and decreased health-related quality of life (HRQOL), but many factors that may contribute to this risk are unknown. Sleep disturbances may be one previously unidentified factor that contributes to this risk.

METHODS AND RESULTS: We analyzed data from the Pediatric Heart Network Fontan cross-sectional study to evaluate associations between a parent or child report of sleep disturbance with reported neurodevelopmental concerns and HRQOL in 558 children with Fontan circulation. Parent-reported sleep disturbance was present in 11% of participants and child-reported sleep disturbance was present in 15%. Parent-reported sleep disturbance was associated with a significantly higher risk of attention problems, anxiety, depression, behavioral problems, and developmental delay ($P < 0.001$ for all). Similarly, parent-reported disturbance was associated with decreased HRQOL on both parent and child-reported HRQOL ($P < 0.001$ for most domains). Child-reported sleep disturbances were associated with increased odds of anxiety, depression, and attention problems as well as worse HRQOL. These associations were present even after adjustment for cardiac, demographic, and socioeconomic factors that may affect HRQOL and neurodevelopmental status.

CONCLUSIONS: Sleep disturbances in children with Fontan circulation are associated with an increased risk of neurodevelopmental problems as well as reduced HRQOL compared with those without sleep disturbance. Better understanding of sleep disturbances is needed in children with Fontan circulation, as sleep disturbances may represent a reversible cause of neurodevelopmental problems and decreased HRQOL in this population.

Key Words: cognitive impairment ■ Fontan procedure ■ quality of life ■ single ventricle ■ sleep

The Fontan procedure was developed in 1968¹ for the treatment of tricuspid atresia and has led to dramatic improvement in survival for individuals with a variety of underlying single-ventricle cardiovascular physiology, with a 30-year survival rate of 85%.² There are now an estimated 50 000 to 70 000 individuals in the world with Fontan circulation, and 60% of these individuals are children.² While survival has greatly increased, the growing population of individuals

with Fontan circulation are known to be at high risk for significant comorbidities, including decreased health-related quality of life (HRQOL) and increased risk of behavioral and neurodevelopmental problems.^{2,3}

Given the growing population of individuals with Fontan circulation, there has been intense interest in identifying causes of decreased HRQOL and neurodevelopmental problems in individuals with Fontan circulation. Given evidence that early neurodevelopmental

Correspondence to: Daniel Combs, MD, 1501 N. Campbell Avenue, P.O. Box 245073, Tucson, AZ 85724. E-mail: combs89@arizona.edu

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021749>

For Sources of Funding and Disclosures, see page 11.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Sleep disturbances may be a previously unrecognized cause of the known behavioral and health-related quality of life impairment in children with Fontan circulation.

What Are the Clinical Implications?

- Sleep disorders in children have existing efficacious therapies; recognition and treatment of sleep disorders may lead to improved behavioral and health-related quality-of-life outcomes in children with Fontan circulation.

Nonstandard Abbreviations and Acronyms

CHAT	Congenital Heart Adolescent and Teenager Questionnaire
CHQ	Child Health Questionnaire

impairments may be predictive of future neurocognitive status and HRQOL,⁴ recognition of causes of neurodevelopmental and HRQOL impairment in children is of particular importance. While there have been numerous studies investigating causes of HRQOL and neurodevelopmental impairment in children with Fontan circulation, it appears that there are many currently unknown factors that may contribute to these impairments. It has been estimated that 70% of the potential causes of neurodevelopmental impairment are currently unknown.⁵ Many of the current identified predictors of neurodevelopmental outcomes, such as genetic factors (genetic syndromes as well as apolipoprotein e2 status), male sex, low birth weight, and socioeconomic status, are difficult to modify or cannot be modified.⁵ Research to date has shown a similar picture for potential modifiers of HRQOL, where patient characteristics are known to be associated with worse HRQOL, but these relationships generally have small effect sizes.³ Thus, it appears that there are other as yet unidentified factors that influence HRQOL in children with Fontan circulation.³ Given this, there is a need to identify other potential causes of neurodevelopmental and HRQOL impairment in children with Fontan circulation, particularly potentially reversible causes of impairment.

Sleep disturbances are a known cause of HRQOL and neurodevelopmental impairment in children,^{6,7} although there are no data specific to children with Fontan circulation. One sleep disturbance, sleep apnea, has previously been shown to be common in

a cohort of school-aged children with moderate to severe congenital heart disease (which included some individuals with Fontan circulation) and associated with neurocognitive impairment, as well as associated with increased mortality in a nationwide sample of infants with congenital heart disease.^{8,9} We hypothesized that sleep disturbances are associated with neurodevelopmental and HRQOL impairment in children with Fontan circulation and examined this association in a very large study of children with Fontan circulation, the Fontan Cross-Sectional Study.

METHODS

The Fontan Cross-Sectional Study was conducted across seven Pediatric Heart Network member centers across the United States and Canada. All data used in this study are freely available via the Pediatric Heart Network website (<https://www.pediatricheartnetwork.org/>). Further details of the study design and methods have been previously published.¹⁰ In brief, children and adolescents (henceforth “children”) aged 6 to 18 years who had a Fontan procedure at least 6 months before enrollment were eligible to participate. Potential participants were excluded if they had significant noncardiac or psychiatric conditions that would prevent successful completion of planned study testing or would invalidate the results of study testing, were pregnant or planning to conceive before completion of study testing or had a primary caregiver who lacked fluency in either Spanish or English. Medical record extractions were performed for all participants. Participants and their parent/caregiver completed questionnaires, participants underwent measurement of serum brain natriuretic peptide levels, echocardiography, cardiopulmonary exercise testing, and cardiac magnetic resonance imaging. All seven Pediatric Heart Network centers obtained local institutional review board or ethics committee approval before initiating the study, and written informed consent was obtained for all subjects from either a parent or a legal guardian or from the subject if of legal age. Subject assent was also obtained per local guidelines.

Parents of participants completed questionnaires about demographics, their child’s health status, and the parent version of the Child Health Questionnaire (CHQ), a validated pediatric general HRQOL instrument.¹¹ The CHQ includes summary scores related to physical and psychosocial well-being as well as 10 sub-domain scores. Scores from the parent-reported CHQ are reported as z scores. Questions about health status asked, “Have you ever been told by a teacher, school official, doctor, nurse, or other health professional that your child has any of the following conditions?” followed by a list of medical conditions as well as behavioral concerns. Answers were recorded as yes/no. For

this analysis, if parents answered yes to “sleep disturbance,” participants were considered to have a sleep disturbance. Relevant demographic items included in this analysis include parent-reported child’s sex, age, family income, and parent educational level. Relevant items extracted from the child’s medical record included pre-Fontan cardiac diagnosis (sorted into categories by Pediatric Heart Network investigators) as well as ventricular dominance. We additionally reviewed reported medications to identify participants taking medications for attention deficit hyperactivity disorder (ADHD), including stimulants or atomoxetine, or other psychiatric medications (antidepressants or antipsychotics).

Children aged 10 to 18 years additionally completed the CHQ-CF87, the child-report version of the CHQ, as well as the Congenital Heart Adolescent and Teenage Questionnaire (CHAT). The child-report CHQ is a validated general pediatric HRQOL measure and includes similar subdomains to the parent-report version but does not include the summary measures.^{11,12} The child-report CHQ is scored from 0 to 100 with higher scores indicating better function. There is a known upwardly skewed distribution that may result in ceiling effects. The CHAT is a validated congenital heart disease-specific HR-QOL instrument with 5 domains on physical, emotional, and social well-being.^{13,14} Scale domain scores range from 0 to 100, with higher values indicating worse functioning. There is a similarly skewed distribution to the CHQ that may result in ceiling effects.

We additionally evaluated child report of sleep disturbance in children age 10 to 18 years by using a question from the child-completed CHQ. Specifically, children answered the question “During the past 4 weeks, how much of the time did you have trouble sleeping?” Answers included “not at all,” “a little of the time,” “some of the time,” “most of the time,” or “all of the time.” We converted this to a categorical variable by classifying those who answered “most of the time” or “all of the time” as having a child-reported sleep problem, while those who answered “not at all,” “a little of the time,” or “some of the time” were classified as not having a child-reported sleep problem. This approach was used to provide a more direct correlate to the yes/no parent question about sleep problems as well as to conserve statistical power given that only approximately half of the study population was old enough to complete the child questionnaires. We performed additional sensitivity analysis using the child report as originally reported as an ordinal variable.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS 27 (IBM, Armonk, NY). Pearson χ^2 tests (or Fisher exact tests if >20% of cells had an expected value <5) were used

to compare categorical outcomes while assessing for baseline differences between children with and without reported sleep problems. Continuous outcome variable normality was assessed using the Shapiro-Wilk test. Consistent with prior report, all continuous outcomes (CHQ and CHAT scores) were nonnormally distributed.¹⁵ Therefore, the Wilcoxon rank-sum test was used for comparison of continuous outcomes between children with and without reported sleep problems. Prior evidence has shown that linear regression/analysis of covariance is not significantly biased compared with nonparametric approaches in most cases for evaluation of non-Gaussian data.¹⁶ Therefore, to account for potential covariates that may affect HRQOL, we additionally performed linear regression to evaluate the relationship between the presence of sleep disturbance and HRQOL with adjustment for age, sex, pre-Fontan cardiac diagnosis, family income, and parent level of education. These covariates were selected as age, sex, congenital heart disease complexity, family income, and parent education level have all previously been associated with an increased likelihood of worse HRQOL.^{17,18} Logistic regression was performed to compare the odds of parent-reported behavioral problems between children with and without reported sleep disturbance and adjust for age, sex, pre-Fontan cardiac diagnosis, family income, and parent level of education. We performed an additional exploratory analysis with the additional inclusion of the CHQ parental emotional impact scale as a covariate to account for the possibility that parents with a higher emotional impact may be more likely to report the presence of behavioral problems in general. We additionally evaluated the relationship between parent report of a sleep problem and the odds of receiving an ADHD or psychiatric medication using logistic regression. We used logistic regression to evaluate the association between parent report of attention problems and the odds of reporting an ADHD medication as well as parent report of depression or anxiety and the odds of reporting a psychiatric medication as well. Cohen’s kappa was used to evaluate the agreement between parent and child report of a sleep problem. We performed additional sensitivity analyses evaluating the combination of parent and child report of a sleep disturbance. We compared individuals with both a parent and child report of a sleep disturbance with those with no report of a sleep disturbance or only either parent or child report of a sleep disturbance. We also compared individuals with either parent or child report of a sleep disturbance compared with individuals without parent or child report of a sleep disturbance. Finally, given the bidirectional association between developmental delays, ADHD and psychiatric disorders, and sleep disturbances,^{19–23} we performed an additional analysis of HRQOL excluding participants whose parents

reported use of ADHD medications, psychiatric medications, or developmental delay. These analyses were restricted to only the sample that included child report. All statistical tests were 2-sided and a P value <0.05 was considered significant.

RESULTS

Parent-reported data were available from 558 participants in the study, and child-reported data were available from 308 participants for the CHQ and 303 for the CHAT. Sleep disturbance was reported by parents in 11% of participants. Demographic information is presented in Table 1. Children with reported sleep disturbance were slightly older (12.8 ± 3.5 versus 11.8 ± 3.4 years old; $P=0.04$). There were no significant differences in sex, race, ethnicity, body mass index, parent education level, or family income. There were some differences in the underlying pre-Fontan diagnosis between children with reported sleep problems compared with those without sleep problems, but there was no significant difference in ventricular dominance between children with reported sleep problems compared with those without.

Parent report of a sleep disturbance was strongly associated with an increased risk of parent-reported behavioral concerns (Figure 1). Sleep disturbance was strongly associated with an increased risk of attention problems, anxiety problems, behavioral problems, depression, developmental delay learning problems, and speech problems ($P<0.001$ for all except speech problems in both adjusted and unadjusted analysis). The strongest association was present between report of sleep disturbance and mood concerns, with 10-fold increased odds of reporting depression or anxiety in unadjusted analysis and even higher odd in the adjusted analysis (adjusted odds ratio [aOR], 26 for anxiety and 16 for depression). Complete details are presented in Table 2.

Inclusion of parent emotional impact from the CHQ had only a slight impact on these results. Sleep disturbance remained associated with higher odds of attention problems (aOR, 4.9; 95% CI, 2.1–11; $P<0.001$), anxiety problems (aOR, 15.6; 95% CI, 6.8–35.4; $P<0.001$), behavioral problems (aOR, 3.0; 95% CI, 1.5–6.3; $P=0.003$), depression (aOR, 12.8; 95% CI, 5.1–37.7; $P<0.001$), developmental delay (aOR, 4.7; 95% CI, 2.3–9.6; $P<0.001$), and learning problems (aOR, 4.6; 95% CI, 2.0–10.6). The association between sleep disturbance and speech problems was no longer significant (aOR, 1.9; 95% CI, 0.9–3.8; $P=0.08$).

Fifteen percent of children self-reported a sleep problem. There was fair agreement between child report of trouble sleeping and parent report of a sleep disturbance (kappa, 0.340; $P<0.001$). We found that

Table 1. Characteristics of Children With Fontan Circulation With and Without Parent-Reported Sleep Disturbance

	Sleep disturbance (N=57)	No sleep disturbance (N=501)	P value
Female sex, %	37	40	0.61
Race, %			0.17
White	96	86	
Black	2	10	
Asian	0	3	
American Indian or Alaskan native	2	1	
Hispanic/Latino ethnicity	6	7	0.69
Age	$11.8\pm 3.4^*$	$12.8\pm 3.5^*$	0.04*
Body mass index percentile	51 ± 32	49 ± 30	0.66
Parent education level, %			0.49
Some high school or less	4	7	
High school graduate or GED	25	25	
Some college, vocational school or 2-y degree	44	33	
4-y college graduate	18	24	
Graduate degree	11	11	
Family income, %			0.27
<\$20 000	22	11	
\$20 000 to \$39 000	16	18	
\$40 000 to \$59 000	14	17	
\$60 000 to \$79 000	14	15	
\$80 000 to \$99 000	8	15	
>\$100 000	28	24	
Anatomic diagnosis, %			0.005*
Single ventricle, double-inlet left ventricle	19	14	
Single ventricle, double-inlet right ventricle	2	1	
Single ventricle, mitral atresia	16	6	
Single ventricle, tricuspid atresia	19	23	
Single ventricle, unbalanced atrioventricular canal defect	9	3	
Single ventricle, heterotaxia syndrome	9	7	
Hypoplastic left heart syndrome	12	21	
Other functional single ventricle	14	25	
Dominant ventricle, %			0.83
Left	49	45	
Right	33	37	
Both	18	18	
Taking ADHD medications, %	23*	5*	$<0.001^*$
Taking psychiatric medications, %	19*	2*	$<0.001^*$

(Continued)

Table 1. Continued

	Sleep disturbance (N=57)	No sleep disturbance (N=501)	P value
Attention problems, %	77*	42*	<0.001*
Anxiety problems, %	59*	12*	<0.001*
Behavioral problems, %	48*	20*	<0.001*
Depression	36*	6*	<0.001*
Developmental delay, %	56*	20*	<0.001*
Learning problems, %	80*	37*	<0.001*
Speech problems, %	42*	25*	0.001*

Data are presented as mean±standard deviation for continuous variables and as percentages for categorical values. ADHD medications included stimulants and atomoxetine. Psychiatric medications included antidepressants and antipsychotics. P values are derived using t tests for continuous variables and χ^2 tests for categorical variables. Because of missing data, sample size is slightly smaller for some variables: race (n=498), ethnicity (n=499), age (n=505), body mass index (n=502), parent education level (n=556) and family income (n=483). ADHD indicates attention deficit hyperactivity disorder; and GED, General Educational Development.

*Indicates $P<0.05$.

while relationships were generally less significant between child report of a sleep disturbance and parent report of behavioral problems, there were still strong associations present in the areas with the strongest association between parent-reported sleep disturbance and behavioral concerns, in particular mood concerns, as well as problems with attention (Table 2).

Parent report of sleep disturbance was associated with increased odds of reporting use of medications for ADHD (OR, 6.4; $P<0.001$) as well as use of psychiatric medications (OR, 15.2; $P<0.001$). Similar results were found in adjusted analysis. Complete details are available in Table 2. As expected, we found a strong relationship between parent report of attention problems and reported use of medications for ADHD (OR, 14.7; 95% CI, 4.5–48.6; $P<0.001$) as well as parent report of depression or anxiety and use of other psychiatric

medications (OR, 15.3; 95% CI, 5.6–42.1; $P<0.001$ for depression; OR, 27.4; 95% CI, 7.7–97.8; $P<0.001$ for anxiety).

Parent report of a sleep disturbance was associated with lower (worse) scores across all domains of the parent-completed CHQ. These associations were present in both unadjusted and adjusted analyses as detailed in Table 3. For most domains, children with a reported sleep disturbance were ≈ 1 z score below children without a reported sleep disturbance ($P<0.001$ for all domains in both unadjusted and adjusted analyses). For the physical summary norm score, children with a reported sleeping disturbance had an unadjusted median score of 36.9 (interquartile range, 28.1–47.5) and adjusted mean score of 36.5 (95% CI, 33.3–39.7) compared with an unadjusted median score of 50.0 (interquartile range, 42.2–53.9) and adjusted mean score of 46.1 (95% CI, 44.9–47.4) in children without a sleep disturbance.

Child-reported HRQOL was worse in children with a parent report of a sleep disturbance as well. On the child-completed CHQ, children with a parent-reported sleep disturbance scored significantly worse (lower scores) compared with children without a parent-reported sleep disturbance on the subscales of physical functioning, emotional and physical role/social limits, bodily pain, behavior, mental health, self-esteem, and general health perceptions in unadjusted analysis. In adjusted analysis, these associations were still significant for subscales except self-esteem. Further details are available in Table 4.

Similarly, on the CHAT, a congenital heart disease-specific HRQOL measure, parent report of a sleep disturbance was associated with higher (worse) scores. Report of a sleep disturbance was associated with more activity limitations, emotional concerns, friendship problems, career concerns and symptom discomfort in unadjusted analysis. Except for friendship problems,

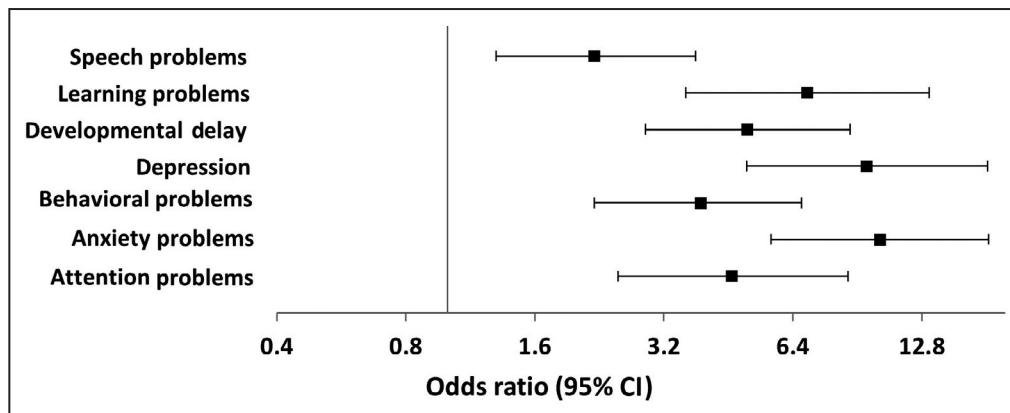


Figure 1. Parent report of sleep disturbance is associated with higher odds of behavioral concerns in children with Fontan circulation. Odds ratios presented are unadjusted, $P<0.001$ for all.

Table 2. Association Between Parent-Reported and Child-Reported Sleep Disturbance and Parent-Reported Behavioral Concerns and Related Medication Use in Children With Fontan Circulation

	Unadjusted		Adjusted	
	Odds ratio	P value	Odds ratio	P value
Parent report				
Attention problems	4.6 (2.5–8.6)*	<0.001*	6.2 (2.8–13.7)*	<0.001*
Anxiety problems	10.2 (5.7–18.3)*	<0.001*	26.0 (11.1–61.2)*	<0.001*
Behavioral problems	3.9 (2.2–6.7)*	<0.001*	4.1 (2.0–8.5)*	<0.001*
Depression	9.5 (5.0–18.2)*	<0.001*	16.1 (5.9–44.1)*	<0.001*
Developmental delay	5.0 (2.9–8.7)*	<0.001*	6.7 (3.3–13.7)*	<0.001*
Learning problems	6.9 (3.6–13.3)*	<0.001*	6.5 (3.0–14.3)*	<0.001*
Speech problems	2.2 (1.3–3.8)*	0.01*	2.3 (1.2–4.7)*	0.02*
ADHD medications	6.4 (2.9–14.0)*	<0.001*	10.1 (3.8–26.7)*	<0.001*
Psychiatric medications	15.2 (5.2–45.0)*	<0.001*	19.0 (4.9–74.6)*	<0.001*
Child report				
Attention problems	1.9 (1.0–3.6)*	0.04*	2.4 (1.2–4.9)*	0.02*
Anxiety problems	4.1 (2.1–8.0)*	<0.001*	4.9 (2.3–10.7)*	<0.001*
Behavioral problems	1.6 (0.8–3.2)	0.17	1.7 (0.8–3.9)	0.19
Depression	3.4 (1.6–7.5)*	0.002*	3.6 (1.5–8.7)*	0.004*
Developmental delay	1.2 (0.6–2.4)	0.66	1.6 (0.7–3.5)	0.27
Learning problems	1.5 (0.8–2.7)	0.19	2.0 (1.0–3.9)	0.052
Speech problems	1.0 (0.5–2.0)	0.95	1.3 (0.6–2.9)	0.53
ADHD medications	2.7 (1.04–7.0)*	0.04*	6.9 (1.9–24.7)*	0.003*
Psychiatric medications	2.1 (0.5–8.5)	0.27	9.9 (1.4–69.8)*	0.02*

Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income, and parent level of education as covariates. ADHD indicates attention deficit hyperactivity disorder.

*Indicates $P < 0.05$.

these associations were present in adjusted analysis as well. Further details are available in Table 4. We additionally found that child report of sleep disturbance

was strongly associated with worse HRQOL across all domains of the CHAT (Table 5). Given that we used a question from the child-reported CHQ to identify sleep

Table 3. Parent-Reported Child Health Questionnaire Domain z Scores in Children With Fontan Circulation With and Without Parent-Reported Sleep Disturbance

	Unadjusted			Adjusted		
	Sleep disturbance	No sleep disturbance	P value	Sleep disturbance	No sleep disturbance	P value
Physical functioning	-1.1 (-2.2 to -0.1)*	-0.1 (-0.8 to 0.6)*	<0.001*	-1.1 (-1.5 to -0.8)*	-0.3 (-0.4 to -0.2)*	<0.001*
Role/social limits–emotional	-0.6 (-2.4 to 0.4)*	0.5 (-0.6 to 0.5)*	<0.001*	-1.3 (-1.7 to -0.8)*	-0.4 (-0.6 to -0.3)*	<0.001*
Role/social limits–physical	-1.3 (-2.2 to 0.4)*	0.4 (-0.4 to 0.4)*	<0.001*	-1.2 (-1.6 to -0.8)*	-0.3 (-0.4 to -0.1)*	0.001*
Bodily pain	-0.9 (-1.9 to 0.1)*	0.5 (-0.4 to 1.0)*	<0.001*	-0.8 (-1.1 to -0.6)*	0.2 (0.1 to 0.3)*	<0.001*
General behavior	-0.7 (-1.5 to 0.3)*	0.3 (-0.5 to 0.9)*	<0.001*	-0.7 (-1.1 to -0.4)*	0.1 (-0.1 to 0.2)*	<0.001*
Mental health	-0.9 (-2.0 to -0.2)*	0.2 (-0.9 to 0.6)*	<0.001*	-1.0 (-1.3 to -0.7)*	0.0 (-0.2 to 0.1)*	<0.001*
Self-esteem	-0.5 (-1.3 to 0.0)*	0.0 (-0.7 to 0.7)*	<0.001*	-0.7 (-0.9 to -0.4)*	-0.1 (-0.3 to 0.0)*	0.001*
General health perceptions	-1.2 (-2.1 to -0.6)*	-0.6 (-1.3 to 0.0)*	<0.001*	-1.3 (-1.5 to -1.0)*	-0.7 (-0.8 to -0.6)*	0.005*
Parental impact–emotional	-1.9 (-2.3 to -0.9)*	-0.3 (-1.5 to 0.4)*	<0.001*	-1.5 (-1.9 to -1.2)*	-0.6 (-0.7 to -0.4)*	<0.001*
Parental impact–time	-0.8 (-1.9 to 0.8)*	0.8 (-0.8 to 0.8)*	<0.001*	-1.0 (-1.3 to -0.6)*	-0.1 (-0.2 to 0.1)*	<0.001*
Physical summary score	-1.3 (-2.2 to -0.2)*	0.0 (-0.8 to 0.4)*	<0.001*	-1.3 (-1.7 to -1.0)*	-0.4 (-0.5 to -0.3)*	<0.001*
Psychosocial summary score	-0.9 (-1.9 to 0.0)*	0.0 (-0.8 to 0.7)*	<0.001*	-1.1 (-1.3 to -0.8)*	-0.2 (-0.3 to -0.1)*	<0.001*

Data are presented as median (interquartile range) for unadjusted data and mean (95% CI) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates.

*Indicates $P < 0.05$.

Table 4. Child-Reported Health-Related Quality of Life in Children with Fontan Circulation With and Without Parent-Reported Sleep Disturbance

	Unadjusted			Adjusted		
	Sleep disturbance	No sleep disturbance	P value	Sleep disturbance	No sleep disturbance	P value
Child Health Questionnaire						
Physical functioning	85.2 (68.5–96.2)*	92.1 (81.5–96.3)*	0.048*	82.4 (77.9–87.0)*	87.6 (85.9–89.2)*	0.04*
Role/social limits–emotional	88.9 (55.5–100)*	100 (88.9–100)*	0.007*	75.6 (68.4–82.8)*	90.0 (87.4–92.6)*	<0.001*
Role/social limits–behavioral	100 (83.3–100)	100 (100–100)	0.63	91.3 (83.7–98.9)	93.3 (90.6–96.0)	0.63
Role/social limits–physical	100 (66.7–100)*	100 (100–100)*	0.02*	82.1 (76.7–87.6)*	92.2 (90.2–94.2)*	0.001*
Bodily pain	70.0 (40.0–80.0)*	80.0 (70–100)*	<0.001*	57.1 (49.0–65.1)*	80.5 (77.6–83.4)*	<0.001*
Behavior	69.7 (63.8–78.5)*	80.9 (71.2–86.9)*	0.006*	71.0 (66.1–75.9)*	78.5 (76.7–80.2)*	0.006*
Mental health	68.8 (56.3–77.3)*	78.1 (70.3–92.2)*	0.002*	66.8 (61.8–71.8)*	77.2 (75.3–79.0)*	0.002*
Self-esteem	75.0 (68.5–85.7)*	83.9 (73.2–92.9)*	0.009*	78.0 (72.4–83.6)	80.9 (78.9–83.0)	0.34
General health perceptions	56.7 (43.5–70.6)*	67.5 (57.1–80.0)*	0.002*	58.7 (52.6–64.9)*	65.9 (63.6–68.1)*	0.03*
Family activities	83.3 (62.5–95.8)	87.5 (70.8–100)	0.12	74.6 (66.6–82.7)	81.6 (78.6–84.5)	0.11
Congenital Heart Adolescent and Teenager Questionnaire						
Activity limitations	16.7 (8.3–30.2)*	8.3 (4.2–20.8)*	0.003*	20.2 (15.3–25.2)*	15.6 (13.8–17.4)*	0.08*
Emotional concerns	29.7 (18.8–44.5)*	17.2 (6.3–31.3)*	0.001*	30.8 (24.0–37.7)*	20.8 (18.3–23.2)*	0.008*
Friendship problems	0 (0–27.1)*	0 (0–8.3)*	0.03*	10.2 (5.0–15.6)	5.7 (3.8–7.6)	0.11
Career concerns	27.5 (13.8–41.3)*	10.0 (5.0–20.0)*	<0.001*	25.7 (19.5–31.9)*	14.9 (12.7–17.2)*	0.002*
Symptom discomfort	9.5 (5.0–18.0)*	4.0 (2.0–8.0)*	<0.001*	11.9 (9.5–14.2)*	6.1 (5.2–6.9)*	<0.001*

Data is presented as median (interquartile range) for unadjusted data and mean (95% CI) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income, and parent level of education as covariates. Higher scores on the Child Health Questionnaire indicate better quality of life, while higher scores on the Congenital Heart Adolescent and Teenager Questionnaire indicate worse quality of life. Child-reported data were available from 308 participants for the Child Health Questionnaire and 303 for the Congenital Heart Adolescent and Teenager Questionnaire.

*Indicates $P < 0.05$.

disturbance, we did not evaluate the association between child-reported sleep disturbance and HRQOL as measured by the CHQ.

Use of child report of frequency of trouble sleeping as an ordinal variable (categories including “all of the time,” “most of the time,” “some of the time,” “a little of the time,” and “none of the time”) generally showed a dose-response for increased frequency of sleep

problems for most outcomes that were significant in the dichotomous analysis. Five percent of children reported trouble sleeping all of the time, 10% reported trouble sleeping most of the time, 20% reported trouble sleeping some of the time, 18% reported trouble sleeping a little of the time, and 47% reported trouble sleeping none of the time. Figure 2 shows the association between increased frequency of trouble sleeping and

Table 5. Child Reported Health-Related Quality of Life in Children With Fontan Circulation With and Without Child-Reported Sleep Disturbance

	Unadjusted			Adjusted		
	Sleeping problem	No sleeping problem	P value	Sleeping problem	No sleeping problem	P value
Congenital Heart Adolescent and Teenager Questionnaire						
Activity limitations	16.7 (8.3–29.2)*	8.3 (0.0–20.8)*	0.001*	20.1 (16.2–24.1)*	15.1 (13.2–16.9)*	0.02*
Emotional concerns	31.3 (18.8–40.6)*	15.6 (6.3–28.1)*	<0.001*	32.0 (26.7–37.2)*	20.2 (17.8–22.7)*	<0.001*
Friendship problems	0.0 (0.0–25.0)*	0.0 (0.0–8.3)*	0.02*	14.3 (9.7–19.0)*	5.5 (3.4–7.7)*	0.001*
Career concerns	25.0 (10.0–35.0)*	10.0 (5.0–20.0)*	<0.001*	25.4 (20.6–30.2)*	14.5 (12.3–16.7)*	<0.001*
Symptom discomfort	9.0 (5.3–17.0)*	4.0 (2.0–7.25)*	<0.001*	10.6 (8.6–12.6)*	5.7 (4.8–6.6)*	<0.001*

Data are presented as median (interquartile range) for unadjusted data and mean (95% CI) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income, and parent level of education as covariates. Higher scores on the Congenital Heart Adolescent and Teenager Questionnaire indicate worse quality of life. Child-reported data were available from 303 participants. Given that a question from the child-reported Child Health Questionnaire was used to identify sleep disturbance, we did not evaluate the association between child-reported sleep disturbance and health-related quality of life as measured by the Child Health Questionnaire.

*Indicates $P < 0.05$.

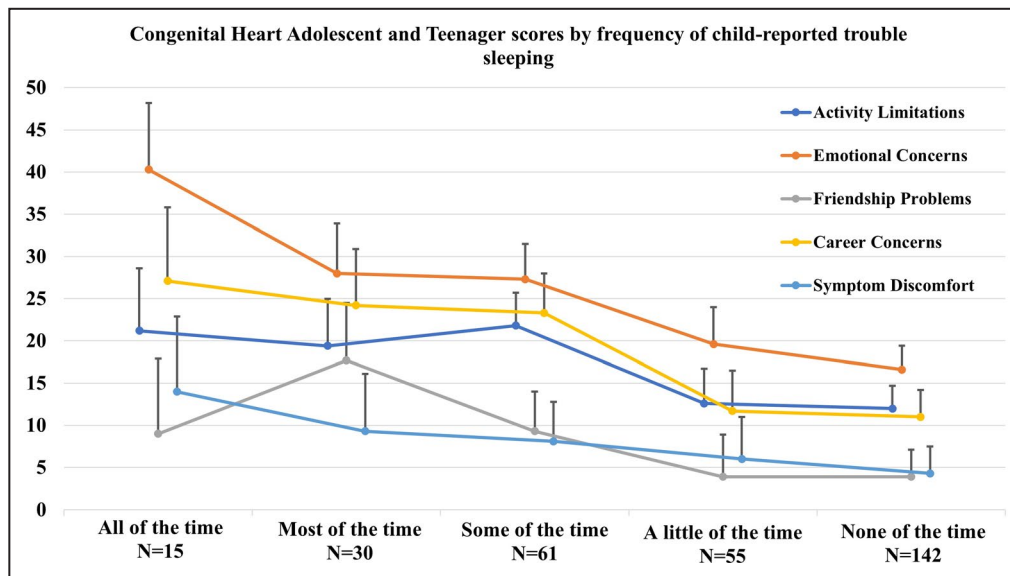


Figure 2. Increased frequency of child reported sleep is associated with worse health-related quality of life as measured by the Congenital Heart Adolescent and Teenager Questionnaire. Results adjusted for age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education; *P* value for trend as determined by linear regression/analysis of covariance was <0.05 for all. Error bars indicate 95% CI.

HRQOL as measured by the CHAT. Complete results of this analysis are presented in Tables S1 through S7.

The remaining sensitivity analyses were similar to the primary analyses. In participants with data for both child and parent report, 5% had both a child and parent report of sleep disturbance, while 20% of participants had either a child or parent report of sleep disturbance. In general, for participants with both a parent- and child-reported sleep disturbance, a greater effect was seen (larger odds ratios and worse HRQOL scores) compared with the effect seen for sensitivity analysis including participants with either a parent- or child-reported sleep disturbance. For analysis excluding participants with reported use of ADHD medications, psychiatric medications, or developmental delay, 15% had either a parent- or child-reported sleep disturbance. Both parent- and child-reported HRQOL was significantly worse in participants with a reported sleep disturbance compared with those without a sleep disturbance. Complete results of sensitivity analyses are available in Tables S1 through S7.

DISCUSSION

Sleep disturbances were reported by a parent for 11% of participants and were self-reported by 15% of children in the study. The presence of a parent-reported sleep disturbance was strongly associated with increased odds of a behavioral concern or neurodevelopmental concern as well as increased odd of use of

ADHD and other psychiatric medications. In this study, parent-reported sleep disturbance was associated with an ≈ 10 -fold increased odds of a reported mood disorder (anxiety or depression) and a ≈ 5 -fold increased odds of a neurodevelopmental concern such as developmental delay, learning problems, or attention problems. While of a smaller magnitude, a similar pattern of increased odds of behavioral and neurodevelopmental concerns was associated with child report of a sleep disturbance. Additionally, parent- and child-reported sleep disturbances were associated with decreased HRQOL in children with Fontan circulation. This association was present even after adjustment for cardiac, demographic, and socioeconomic factors likely to affect HRQOL.

To provide perspective on the results of this study, a large ($n > 150\,000$) prior study using medical record review identified a diagnosis of a sleep problem in 4% of children,²⁴ compared with the 10% reported incidence of a parent-reported sleep diagnosis in the Fontan study. It should be noted that there are differences in methodology (medical record extraction versus parent report of a diagnosis) that limit this comparison. In a prior study of insomnia in a community cohort of adolescents (aged ≈ 10 –18 years), 12% of participants self-reported having difficulty staying asleep,²⁵ a similar single question to the question used in this study, as compared with 15% of participants in the Fontan study. Overall, this suggests that the prevalence of sleep disturbances is similar or somewhat more common in children with Fontan circulation as compared with general population-based studies.

It appears that the association of sleep problems with worse outcomes is stronger in children with Fontan circulation compared with children without Fontan circulation. In the community cohort study of insomnia discussed above, insomnia (either intermittent or persistent) was associated with increased odds of reporting use of a psychiatric medication (OR, 2.9; 95% CI, 1.0–8.3; $P=0.05$). In the Fontan study, parent report of a sleep disturbance was associated with a much greater increased odds of reporting use of a psychiatric medication (OR, 15.2; 95% CI, 5.2–45.0; $P<0.001$). Given the differences between this study and the present study in regard to how the presence of a sleep disturbance was identified, further study is needed to confirm this finding.

Sleep disturbances and behavioral problems (including ADHD, among others) are known to have a bidirectional relationship.^{19–23} Essentially, the presence of behavioral concerns leads to a future increased risk of sleep disturbance, and conversely, the presence of a sleep disturbance leads to a future increased risk of behavioral problems. Treatment of a variety of sleep disorders has been shown to mitigate the associated risk of both mood disorders and neurodevelopmental problems.^{26–28} For example, a recent meta-analysis of nonpharmacologic sleep interventions showed that they had a large effect (Cohen's $d=-0.81$) in reducing depression symptoms.²⁹ Given this, it is feasible that treatment of sleep disturbances, in addition to existing treatments, in children with Fontan circulation may lead to improvement in the known behavioral and neurodevelopmental concerns present in this population.³⁰

Children with Fontan circulation without a parent-reported sleeping disturbance had essentially normal HRQOL as measured by the parent-completed CHQ. Specifically, for all domains, the median/mean z score was within an SD of 0, the healthy population mean. Conversely, for almost all domains, children with Fontan circulation with a parent-reported sleeping disturbance had a z score near -1 , 1 standard deviation below the mean z score of 0 for healthy children. This may shed light on prior research that has had mixed results showing neurodevelopmental or HRQOL impairment in some children with Fontan circulation but not others.^{3,5,31–34} Prior studies of children with Fontan circulation have not included sleep as a potential factor that may impact HRQOL or neurodevelopmental impairments. Given that in this study, only children with a sleep disturbance had decreased HRQOL and were at increased risk of neurodevelopmental concerns, it is conceivable that cohorts that recruited less children with a sleep disturbance did not show significant impairment of HRQOL or neurodevelopment in children with Fontan circulation, while cohorts that recruited more children with a sleep disturbance did show a

significant HRQOL and neurodevelopmental impairment in children with Fontan circulation.

We found that there were fewer significant differences in child-reported HRQOL compared with parent-reported HRQOL in children with Fontan circulation with and without parent-reported sleep disturbance. This difference may be in part explained by the known discrepancy between child and parent report of HRQOL, in which children tend to report higher HRQOL compared with their parents.³⁵ This may lead to ceiling effects, resulting in smaller differences between the 2 groups. Additionally, child-reported HRQOL was available in only approximately half of the sample, as it was collected only from children aged 10 to 18 years. Thus, it is possible that the smaller sample size reduced the statistical significance of some of our findings.

There are multiple strengths to this study. The study population recruited through the Pediatric Heart Network was a large, nationally representative sample of children with Fontan circulation. The CHQ and CHAT are validated pediatric HR-QOL measures that have been used in a variety of other studies.^{14,15,36} We additionally had 2 separate ratings of HRQOL outcomes from both child and parent, which both showed significant differences between children with and without a reported sleep disturbance. Given the potential for discrepancies between parent and child report of HRQOL,³⁷ our results are striking given that both parent and child report of HRQOL was significantly worse in children with a reported sleep disturbance across almost all domains. We were additionally able to evaluate both parent and child report of sleep disturbance and found generally consistent associations between parent and child report of sleep disturbance with behavioral problems as well as HRQOL. Additionally, we performed adjusted analysis to account for cardiac, demographic, and socioeconomic factors that may impact HRQOL. Inclusion of the relationship between sleep disturbance and ADHD and other psychiatric medications provided additional support that parent-reported sleep disturbance was associated with significant behavioral and neurodevelopmental problems. Additionally, the strong relationship observed between parent-reported attention problems with ADHD medications as well as parent-reported depression or anxiety with psychiatric medications demonstrates that parent report was reflective of problems requiring medical attention.

There are limitations to our study as well. The use of linear regression for adjusted analysis in our sample likely had reduced statistical efficiency and resulting larger (less significant) P values as compared with the unadjusted nonparametric analysis. This may explain the differences in some of the P values in the adjusted versus unadjusted analysis, which resulted in some outcomes having statistical significance in

unadjusted analysis but not in the adjusted analysis. We also chose to not correct for multiple comparisons given that this is hypothesis-generating research rather than a definitive study meant to conclusively address the topic of sleep disturbances in children with Fontan circulation. Additionally, it is possible that children with severe behavioral disturbances may have been excluded from study participation because of inability to complete study procedures such as cardiac imaging or exercise testing, which may have led to a cohort with fewer children with severe behavioral problems. This potential selection bias would lower the chance to detect the significance of our findings, given that this would be expected to reduce the overall sample size with behavioral problems. Additionally, there is a risk of model overfitting for our adjusted logistic regression given the relatively small sample of 57 children with parent-reported sleep disturbance. Finally, as this is a cross-sectional study, we are able to determine the presence of a significant association between sleep disturbances and behavioral problems and decreased quality of life but cannot determine the causality of this relationship.

As the Fontan study was not specifically designed to look at sleep disturbances in children with Fontan circulation, we used a single question to determine the presence of a sleep disturbance. This single-question approach has been used successfully in other cohorts to provide important results to guide future research.^{38,39} However, given this limitation, we are not able to determine what specific sleep disturbance may be present in participants with a reported sleep disturbance. Insomnia is common and associated with decreased HRQOL in children without congenital heart disease.²⁵ Similarly, obstructive sleep apnea was found to be prevalent and associated with cognitive impairment in a study of children with congenital heart disease, which included some individuals with Fontan circulation.⁸ The Fontan study did not collect information that would be useful to determine the presence of obstructive sleep apnea. One additional prior study found that 45% of children with Fontan circulation evaluated by a pulmonologist as part of a multidisciplinary clinic reported symptoms of obstructive sleep apnea including snoring, gasping, or pauses in breathing, while an additional 12% reported "other" sleep concerns.⁴⁰ The question used to determine the self-report of a sleep disturbance was targeted to symptoms of insomnia (but would not differentiate primary insomnia versus insomnia secondary to a different underlying sleep disorder). There was fair agreement between self-reported sleep disturbance and parent report of a sleep disturbance (κ , 0.340; $P < 0.001$). A potential cause for this limited agreement is that the child question used to identify the presence of a sleep disturbance asked about insomnia symptoms specifically,

while the parent question used the more general concept of sleep disturbance. Given that the child-report question would be expected to primarily identify insomnia, this level of agreement suggests that insomnia was likely a significant proportion of parent-reported sleep disturbances. Given the literature suggesting that obstructive sleep apnea appears to be the most common disorder clinicians look for in combination with the correlation between child-reported insomnia symptoms and parent report of a sleep disturbance, we hypothesize that obstructive sleep apnea and insomnia were likely the most common underlying conditions represented by report of a sleep disturbance.

The results of the current analysis suggest that sleep disturbances are associated with significantly decreased HRQOL and increased risk of behavioral and neurodevelopmental concerns in children with Fontan circulation. It should also be noted that in this study, the particular question about sleep disturbance asked the parent about being told by a professional that their child had a sleep disturbance, although it is possible parents may have answered yes if they thought their child had a sleep problem even if they have not been told of a sleep disturbance by a professional. Given that screening for sleep disorders by clinicians is generally poor,⁴¹ it is possible that the 11% of children in this study found to have a reported sleep disturbance is an underestimation. Given that potential misclassification of participants would be expected to decrease the magnitude of difference between the 2 groups, this would not decrease the significance of the findings in this study.

We were unable to ascertain what specific sleep disturbance was present in this study; however, all common sleep disorders have existing efficacious therapies. Future studies using validated sleep diagnostic approaches such as actigraphy or polysomnography in addition to sleep-specific validated questionnaires are needed to further clarify what types of sleep disturbances are common in children with Fontan circulation and whether the association between sleep disturbances and decreased HRQOL we have found is present across sleep problems in general or specific to particular sleep disorders.

CONCLUSIONS

Sleep disturbances are strongly associated with both decreased HR-QOL as well as increased odds of behavioral and neurodevelopmental concerns in children with Fontan circulation. Sleep disturbances are amenable to treatment, and treatment of sleep disturbances has been shown to improve HRQOL, behavior, and neurodevelopmental status in children without Fontan circulation, although there are no available data in children with Fontan circulation. Further research is needed to better describe sleep disturbances and

associated HRQOL impairment and risk of neurodevelopmental and behavioral concerns in children with Fontan circulation. Treatment of sleep disturbances may be a potential avenue to improve outcomes in this high-risk population of children.

ARTICLE INFORMATION

Received March 22, 2021; accepted September 15, 2021.

Affiliations

UAHS Center for Sleep & Circadian Sciences (K.K., M.P., N.P., S.L., S.P., D.C.); Department of Pediatrics (M.D.S., S.K., W.J.M., D.C.), Mel and Enid Zuckerman College of Public Health (C.H.) and Department of Psychology (J.E.), University of Arizona, Tucson, AZ; and Sonoran University Center for Excellence in Developmental Disabilities, University of Arizona, Tucson, AZ (J.E.).

Acknowledgments

Data from the Fontan cross-sectional study was provided by the Pediatric Heart Network. Author contributions: DC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KR, MP, MS, SK, JE, WJM, CHH, SL, NP, SP and DC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Sources of Funding

Funding for this project was provided by an American Heart Association Career Development Award (19CDA34740005), National Institutes of Health (HL151254) and a University of Arizona Health Sciences Career Development Award to Dr Combs as well as HL126140 and OT2HL156812 to Dr Parthasarathy. The Fontan Cross-sectional study was funded by HL068270, HL068269, HL068292, HL068290, HL068288, HL068285, HL068281 and HL068279 from the NIH/NHLBI. Role of the sponsors: The sponsors (American Heart Association, National Institutes of Health and University of Arizona Health Sciences) had no input into study design or manuscript development.

Disclosures

Dr Combs reports a grant from the LuMind-IDSC foundation as well as prior funding from the American Academy of Sleep Medicine Foundation. Dr Edgin reports grants from the LuMind Foundation and the National Institutes of Health. Dr Morgan reports funding from NIH, the Cystic Fibrosis Foundation as well as consultant fees from the Cystic Fibrosis Foundation and speaker honoraria from the American Thoracic Society and the American College of Chest Physicians. These relationships are unrelated to this paper. Dr Parthasarathy reports grants from the National Institutes of Health, American Academy of Sleep Medicine Foundation, Patient Centered Outcomes Research Institute, personal royalty fees from UpToDate Inc, and consultant fees from Jazz pharmaceuticals. Outside the submitted work, Dr Parthasarathy has a patent UA 14-018 U.S.S.N. 90 61/884,654; PTAS 502570970 (home breathing device) issued. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1-S7

REFERENCES

- Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240–248. doi: 10.1136/thx.26.3.240
- Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, Hsia T-Y, Hsu DT, Kovacs AH, McCrindle BW, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation*. 2019;140(6):e234–e284. doi: 10.1161/CIR.0000000000000696
- Marshall KH, D'Udekem Y, Sholler GF, Opatowsky AR, Costa DSJ, Sharpe L, Celermajer DS, Winlaw DS, Newburger JW, Kasparian NA. Health-related quality of life in children, adolescents, and adults with a Fontan circulation: a meta-analysis. *J Am Heart Assoc*. 2020;9:e014172. doi: 10.1161/JAHA.119.014172
- Brook JS, Brook DW, Zhang C, Seltzer N, Finch SJ. Adolescent ADHD and adult physical and mental health, work performance, and financial stress. *Pediatrics*. 2013;131:5–13. doi: 10.1542/peds.2012-1725
- du Plessis K, d'Udekem Y. The neurodevelopmental outcomes of patients with single ventricles across the lifespan. *Ann Thorac Surg*. 2019;108:1565–1572. doi: 10.1016/j.athoracsur.2019.05.043
- Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatr Clin North Am*. 2011;58:649–665.
- Hiscock H, Canterford L, Ukoumunne OC, Wake M. Adverse associations of sleep problems in Australian preschoolers: National population study. *Pediatrics*. 2007;119:86–93. doi: 10.1542/peds.2006-1757
- Combs D, Edgin JO, Klewer S, Barber BJ, Morgan WJ, Hsu CH, Abraham I, Parthasarathy S. Obstructive sleep apnea and neurocognitive impairment in children with congenital heart disease. *Chest*. 2020;158:1208–1217. doi: 10.1016/j.chest.2020.03.021
- Combs D, Skrepnek G, Seckeler MD, Barber BJ, Morgan WJ, Parthasarathy S. Sleep-disordered breathing is associated with increased mortality in hospitalized infants with congenital heart disease. *J Clin Sleep Med*. 2018;14:1551–1558. doi: 10.5664/jcs.m.7334
- Sleeper LA, Anderson P, T. Hsu D, Mahony L, McCrindle BW, Roth SJ, Saul JP, Williams RV, Geva T, Colan SD, et al. Design of a large cross-sectional study to facilitate future clinical trials in children with the Fontan palliation. *Am Heart J*. 2006;152:427–433. doi: 10.1016/j.ahj.2006.02.009
- Landgraf JM, Abetz L, Ware JA. *The CHQ user's manual*. Boston, MA: The Health Institute, New England Medical Centre; 1996.
- Waters EB, Salmon LA, Wake M, Wright M, Hesketh KD. The health and well-being of adolescents: a school-based population study of the self-report child health questionnaire. *J Adolesc Health*. 2001;29:140–149. doi: 10.1016/S1054-139X(01)00211-7
- McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, Eisenmann JC. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. *Arch Dis Child*. 2007;92:509–514. doi: 10.1136/adc.2006.105239
- Kendall L, Lewin RJ, Parsons JM, Veldtman GR, Quirk J, Hardman GE. Factors associated with self-perceived state of health in adolescents with congenital cardiac disease attending paediatric cardiologic clinics. *Cardiol Young*. 2001;11:431–438. doi: 10.1017/S1047951101000555
- McCrindle BW, Zak V, Pemberton VL, Lambert LM, Vetter VL, Lai WW, Uzark K, Margossian R, Atz AM, Cook A, et al. Functional health status in children and adolescents after Fontan: comparison of generic and disease-specific assessments. *Cardiol Young*. 2014;24:469–477. doi: 10.1017/S1047951113000632
- Vickers AJ. Parametric versus non-parametric statistics in the analysis of randomized trials with non-normally distributed data. *BMC Med Res Methodol*. 2005;5:35. doi: 10.1186/1471-2288-5-35
- Ernst MM, Marino BS, Cassidy A, Piazza-Waggoner C, Franklin RC, Brown K, Wray J. Biopsychosocial predictors of quality of life outcomes in pediatric congenital heart disease. *Pediatr Cardiol*. 2018;39:79–88. doi: 10.1007/s00246-017-1730-6
- Xiang L, Su Z, Liu Y, Huang Y, Zhang X, Li S, Zhang H. Impact of family socioeconomic status on health-related quality of life in children with critical congenital heart disease. *J Am Heart Assoc*. 2019;8:e010616. doi: 10.1161/JAHA.118.010616
- Insomnia BDJ. Insomnia, depression and aging. Assessing sleep and mood interactions in older adults. *Geriatrics*. 2004;59:47–51; quiz 52.
- Owens JA. A clinical overview of sleep and attention-deficit/hyperactivity disorder in children and adolescents. *J Can Acad Child Adolesc Psychiatry*. 2009;18:92–102.
- Shanahan L, Copeland WE, Angold A, Bondy CL, Costello EJ. Sleep problems predict and are predicted by generalized anxiety/depression and oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53:550–558. doi: 10.1016/j.jaac.2013.12.029
- Gregory AM, Caspi A, Eley TC, Moffitt TE, O'Connor TG, Poulton R. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *J Abnorm Child Psychol*. 2005;33:157–163. doi: 10.1007/s10802-005-1824-0
- Um YH, Hong SC, Jeong JH. Sleep problems as predictors in attention-deficit hyperactivity disorder: causal mechanisms, consequences and treatment. *Clin Psychopharmacol Neurosci*. 2017;15:9–18. doi: 10.9758/cpn.2017.15.1.9

24. Meltzer LJ, Johnson C, Crosette J, Ramos M, Mindell JA. Prevalence of diagnosed sleep disorders in pediatric primary care practices. *Pediatrics*. 2010;125:e1410–e1418. doi: 10.1542/peds.2009-2725
25. Combs D, Goodwin JL, Quan SF, Morgan WJ, Shetty S, Parthasarathy S. Insomnia, health-related quality of life and health outcomes in children: a seven year longitudinal cohort. *Sci Rep*. 2016;6:27921. doi: 10.1038/srep27921
26. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, Marcus CL, Guire KE. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics*. 2006;117:e769–e778. doi: 10.1542/peds.2005-1837
27. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatr Neurol*. 2000;22:182–186. doi: 10.1016/S0887-8994(99)00152-6
28. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *J Pineal Res*. 2009;47:1–7. doi: 10.1111/j.1600-079X.2009.00681.x
29. Gee B, Orchard F, Clarke E, Joy A, Clarke T, Reynolds S. The effect of non-pharmacological sleep interventions on depression symptoms: a meta-analysis of randomised controlled trials. *Sleep Med Rev*. 2019;43:118–128. doi: 10.1016/j.smrv.2018.09.004
30. McCrindle BW, Zak V, Breitbart RE, Mahony L, Shrader P, Lai WW, Burns KM, Colan SD, Williams RV, Goldberg D, et al. The relationship of patient medical and laboratory characteristics to changes in functional health status in children and adolescents after the Fontan procedure. *Pediatr Cardiol*. 2014;35:632–640. doi: 10.1007/s00246-013-0831-0
31. Bellinger DC, Watson CG, Rivkin MJ, Robertson RL, Roberts AE, Stopp C, Dunbar-Masterson C, Bernson D, DeMaso DR, Wypij D, et al. Neuropsychological status and structural brain imaging in adolescents with single ventricle who underwent the Fontan procedure. *J Am Heart Assoc*. 2015;4:e002302. doi: 10.1161/JAHA.115.002302
32. Forbess JM, Visconti KJ, Bellinger DC, Jonas RA. Neurodevelopmental outcomes in children after the Fontan operation. *Circulation*. 2001;104:1127–1132. doi: 10.1161/hc37t1.094816
33. Sugimoto A, Ota N, Ibuki K, Miyakoshi C, Murata M, Tosaka Y, Yamazaki T, Sakamoto K. Risk factors for adverse neurocognitive outcomes in school-aged patients after the Fontan operation. *Eur J Cardiothorac Surg*. 2013;44(3):454–461; discussion 461. doi: 10.1093/ejcts/ezt062
34. Wernovsky G, Stiles KM, Gauvreau K, Gentles TL, duPlessis AJ, Bellinger DC, Walsh AZ, Burnett J, Jonas RA, Mayer JE, et al. Cognitive development after the Fontan operation. *Circulation*. 2000;102:883–889. doi: 10.1161/01.CIR.102.8.883
35. Lambert LM, Minich LL, Newburger JW, Lu M, Pemberton VL, McGrath EA, Atz AM, Xu M, Radojewski E, Servedio D, et al.; Pediatric Heart Network I. Parent- versus child-reported functional health status after the Fontan procedure. *Pediatrics*. 2009;124:e942–e949. doi: 10.1542/peds.2008-1697
36. Walker RE, Gauvreau K, Jenkins KJ. Health-related quality of life in children attending a cardiology clinic. *Pediatr Cardiol*. 2004;25:40–48. doi: 10.1007/s00246-003-0348-z
37. Ruggiero KM, Hickey PA, Leger RR, Vessey JA, Hayman LL. Parental perceptions of disease-severity and health-related quality of life in school-age children with congenital heart disease. *J Spec Pediatr Nurs*. 2018;23. doi: 10.1111/jspn.12204
38. Ustinov Y, Lichstein KL, Wal GS, Taylor DJ, Riedel BW, Bush AJ. Association between report of insomnia and daytime functioning. *Sleep Med*. 2010;11:65–68. doi: 10.1016/j.sleep.2009.07.009
39. Chung KF, Yeung WF, Ho FY. Insomnia identity and its correlates in adolescents. *Sleep Breath*. 2020;24:717–724. doi: 10.1007/s11325-019-01913-4
40. Liptzin DR, Di Maria MV, Younoszai A, Narkewicz MR, Kelly SL, Wolfe KR, Veress LA. Pulmonary screening in subjects after the Fontan procedure. *J Pediatr*. 2018;199:140–143. doi: 10.1016/j.jpeds.2018.03.050
41. Parthasarathy S, Carskadon MA, Jean-Louis G, Owens J, Bramoweth A, Combs D, Hale L, Harrison E, Hart CN, Hasler BP, et al. Implementation of sleep and circadian science: recommendations from the Sleep Research Society and National Institutes of Health Workshop. *Sleep*. 2016;39:2061–2075. doi: 10.5665/sleep.6300

SUPPLEMENTAL MATERIAL

Table S1. Association between parent-reported and child-reported sleep disturbance and parent-reported behavioral concerns and related medication use in children with Fontan circulation.

	Unadjusted		Adjusted	
	Odds ratio	p	Odds ratio	p
Both report				
Attention Problems	3.3 (1.03, 10.4)	0.045	5.7 (1.6, 20.8)	0.008
Anxiety Problems	16.9 (5.2, 54.9)	<0.001	25.1 (6.1, 103.5)	<0.001
Behavioral Problems	2.3 (0.8, 6.7)	0.11	2.7 (0.8, 9.1)	0.1
Depression	17.6 (5.9, 52.8)	<0.001	27.9 (6.9, 112.5)	<0.001
Developmental Delay	3.1 (1.1, 8.9)	0.03	3.2 (1.02, 10.0)	0.046
Learning problems	3.7 (1.2, 11.9)	0.03	4.2 (1.2, 14.3)	0.02
Speech problems	2.1 (0.7, 6.0)	0.17	2.2 (0.7, 7.1)	0.2
ADHD Medications	4.3 (1.3, 14.7)	0.02	14.5 (2.7, 79.0)	0.002
Psychiatric Medications	7.4 (1.8, 31.3)	0.006	133.6 (4.9, 3670)	0.004
Either report				
Attention Problems	3.0 (1.6, 5.6)	0.001	3.9 (1.9, 7.8)	<0.001
Anxiety Problems	6.4 (3.3, 12.4)	<0.001	8.2 (3.7, 18.1)	<0.001
Behavioral Problems	2.5 (1.3, 4.7)	0.005	3.2 (1.5, 6.6)	0.002
Depression	4.8 (2.2, 10.2)	<0.001	6.8 (2.7, 17.0)	<0.001
Developmental Delay	1.9 (0.98, 3.7)	0.06	2.1 (1.004, 4.2)	0.049
Learning problems	2.6 (1.4, 4.8)	0.002	3.0 (1.5, 5.7)	0.001
Speech problems	1.3 (0.6, 2.4)	0.5	1.3 (0.6, 2.7)	0.5
ADHD Medications	3.4 (1.4, 8.4)	0.006	7.0 (2.3, 21.1)	0.001
Psychiatric Medications	5.1 (1.5, 17.6)	0.009	18.0 (3.2, 102.5)	0.001

For “both report,” both parent and child reported a sleep disturbance to be included in the group with sleep disturbance. For “either report,” children were included if either parent or child reported a sleep disturbance. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates. **Bold** indicates $p < 0.05$.

Table S2. Parent-reported Child Health Questionnaire domain Z- scores in children with Fontan circulation with and without parent-reported sleep disturbance.

	Unadjusted			Adjusted		
	Sleep disturbance	No sleep disturbance	P	Sleep disturbance	No sleep disturbance	P
Both report						
Physical Functioning	-1.1 (-1.8, 0.2)	-0.1 (-0.8, 0.6)	0.004	-1.1 (-1.7, -0.6)	-0.3 (-0.5, -0.2)	0.008
Role/Social Limits-Emotional	0.5 (-2.9, 0.5)	0.5 (-0.6, 0.5)	0.02	-1.7 (-2.3, -1.0)	-0.3 (-0.5, -0.2)	<0.001
Role/Social Limits-Physical	0.4 (-2.2, 0.4)	0.4 (-0.4, 0.4)	0.008	-1.1 (-1.7, -0.5)	-0.2 (-0.4, 0)	0.007
Bodily Pain	-0.9 (-1.9, 0.1)	0.0 (-0.4, 1.0)	<0.001	-1.2 (-1.7, -0.6)	0.1 (0.0, 0.2)	<0.001
General Behavior	-0.6, (-1.2, 0.5)	0.3 (-0.4, 0.9)	0.01	-0.6 (-1.1, -0.1)	-0.6 (-1.1, -0.1)	0.008
Mental Health	-1.2 (-2.0, -0.2)	-0.2 (-0.9, 0.6)	<0.001	-1.3 (-1.8, -0.7)	-0.1 (-0.3, 0)	<0.001
Self Esteem	-0.5 (-1.6, 0)	-0.2 (-0.9, 0.5)	0.28	-0.6 (-1.1, -0.1)	-0.4 (-0.5, -0.2)	0.32
General Health Perceptions	-1.0 (-1.6, -0.4)	-0.6, (-1.3, 0)	0.03	-1.1 (-1.6, -0.6)	-0.7 (-0.8, -0.6)	0.1
Parental Impact-Emotional	-1.9 (-2.2, -0.7)	-0.3 (-1.5, 0.4)	0.001	-1.6 (-2.2, -1.1)	-0.6 (-0.8, -0.5)	0.001
Parental Impact- Time	0.2 (-1.4, 0.8)	0.2 (-0.8, 0.8)	0.12	-0.6 (-1.2, 0.1)	-0.1 (-0.3, 0.1)	0.15
Physical Summary Score	-1.3 (-2.0, -0.4)	0 (-0.8, 0.4)	<0.001	-1.1 (-1.6, -0.5)	-0.4 (-0.5, -0.2)	0.02
Psychosocial Summary Score	-0.7 (-1.9, 0.1)	-0.1 (-0.8, 0.6)	0.04	-1.0 (-1.5, -0.4)	-0.2 (-0.4, -0.1)	0.009
Either report						
Physical Functioning	-0.6 (-1.5, 0.2)	0.2 (-0.8, 0.6)	0.001	-0.7 (-1.0, -0.5)	-0.3 (-0.4, -0.1)	0.006
Role/Social Limits-Emotional	0.5 (-1.5, 0.5)	0.5 (-0.6, 0.5)	0.01	-0.9 (-1.2, -0.5)	-0.3 (-0.5, -0.1)	0.002
Role/Social Limits-Physical	0.4 (-1.3, 0.4)	0.4 (-0.4, 0.4)	0.001	-0.8 (-1.1, -0.4)	-0.1 (-0.3, 0)	0.002
Bodily Pain	-0.4 (-1.4, 0.1)	0.5 (-0.4, 1.0)	<0.001	-0.7 (-1.0, -0.5)	0.3 (0.1, 0.4)	<0.001
General Behavior	-0.5 (-1.3, 0.1)	0.4 (-0.5, 0.9)	<0.001	-0.6 (-0.8, -0.3)	0.2 (0.0, 0.3)	<0.001
Mental Health	-0.9 (-1.6, -0.2)	0.2 (-0.9, 0.6)	<0.001	-0.9 (-1.2, -0.6)	0.0 (-0.2, 0.1)	<0.001
Self Esteem	-0.7 (-1.6, -0.2)	-0.2 (-0.9, 0.5)	<0.001	-0.9 (-1.2, -0.6)	-0.3 (-0.4, -0.1)	<0.001
General Health Perceptions	-1.2 (-1.7, -0.5)	-0.6 (-1.2, 0.1)	<0.001	-1.0 (-1.3, -0.8)	-0.6 (-0.8, -0.5)	0.01
Parental Impact-Emotional	-1.3 (-2.2, -0.7)	-0.3 (-1.5, 0.4)	<0.001	-1.4 (-1.7, -1.1)	-0.5 (-0.7, -0.3)	<0.001
Parental Impact-Time	-0.3 (-1.4, 0.2)	0.8 (-0.3, 0.8)	<0.001	-0.7 (-1.0, -0.3)	0.0 (-0.2, 0.2)	0.001
Physical Summary Score	-0.8 (-1.7, 0.0)	0.2 (-0.6, 0.4)	<0.001	-0.9 (-1.2, -0.6)	-0.3 (-0.4, -0.1)	<0.001
Psychosocial Summary Score	-0.7 (-1.4, -0.3)	0.0 (-0.7, 0.7)	<0.001	-0.9 (-1.2, -0.7)	-0.1 (-0.3, 0.0)	<0.001

For “both report,” both parent and child reported a sleep disturbance to be included in the group with sleep disturbance. For “either report,” children were included if either parent or child reported a sleep disturbance. Data is presented as median (Interquartile range) for unadjusted data and mean (95% confidence interval) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates. **Bold** indicates $p < 0.05$.

Table S3. Child-reported health-related quality of life as measured by the Congenital Heart Adolescent and Teenager questionnaire in children with Fontan circulation with and without parent-reported sleep disturbance.

	Unadjusted			Adjusted		
	Sleep disturbance	No sleep disturbance	P	Sleep disturbance	No sleep disturbance	P
Both report						
Activity Limitations	20.1 (12.5, 31.3)	8.3 (4.2, 20.8)	0.008	22.4 (15.8, 29.0)	15.4 (13.7, 17.2)	0.047
Emotional Concerns	31.3 (23.4, 43.8)	18.8 (6.3, 31.3)	0.001	36.6 (27.9, 45.2)	21.2 (18.9, 23.5)	0.001
Friendship Problems	8.3 (0.0, 33.3)	0.0 (0.0, 8.3)	0.01	18.9 (10.5, 27.3)	5.9 (3.7, 8.1)	0.004
Career Concerns	35.0 (22.5, 47.5)	10.0 (5.0, 20.0)	<0.001	33.9 (26.1, 41.6)	15.1 (13.1, 17.2)	<0.001
Symptom Discomfort	11.0 (6.0, 19.0)	5.0 (2.0, 8.0)	0.001	11.7 (8.6, 14.8)	6.2 (5.4, 7.1)	0.001
Either report						
Activity Limitations	16.7 (8.3, 29.2)	8.3 (0.0, 16.7)	<0.001	19.4 (16.1, 22.9)	14.9 (13.0, 16.7)	0.02
Emotional Concerns	28.1 (17.2, 40.6)	15.6 (6.3, 28.1)	<0.001	30.6 (26.1, 35.2)	19.6 (17.1, 22.0)	<0.001
Friendship Problems	0.0 (0.0, 16.7)	0.0 (0.0, 8.3)	0.04	11.8 (7.8, 15.8)	5.6 (3.4, 7.7)	0.008
Career Concerns	25.0 (10.0, 35.0)	10.0 (0.0, 20.0)	<0.001	24.3 (20.1, 28.6)	13.9 (11.6, 16.2)	<0.001
Symptom Discomfort	8.0 (5.0, 16.5)	4.0 (2.0, 7.0)	<0.001	10.5 (9.0, 12.0)	5.4 (4.5, 6.2)	<0.001

For “both report,” both parent and child reported a sleep disturbance to be included in the group with sleep disturbance. For “either report,” children were included if either parent or child reported a sleep disturbance. Data is presented as median (Interquartile range) for unadjusted data and mean (95% confidence interval) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates. Higher scores on the Congenital Heart Adolescent and Teenager questionnaire indicate worse quality of life. **Bold** indicates $p < 0.05$.

Table S4. Association between broken out child-reported sleep disturbance and parent-reported behavioral concerns and related medication use in children with Fontan circulation.

	Unadjusted				
	Trouble Sleeping?				
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Attention Problems	2.1 (0.7, 6.3)	3.0 (1.3, 7.1)	2.0 (1.1, 3.8)	1.2 (0.6, 2.3)	1.0
Anxiety Problems	3.6 (1.2, 11.2)	3.5 (1.4, 8.6)	0.7 (0.3, 1.9)	1.0 (0.4, 2.4)	1.0
Behavioral Problems	1.2 (0.3, 4.6)	2.3 (0.9, 5.7)	1.3 (0.6, 2.8)	1.8 (0.8, 3.8)	1.0
Depression	4.3 (1.2, 16.1)	4.0 (1.4, 11.6)	1.4 (0.5, 4.0)	1.6 (0.5, 4.5)	1.0
Developmental Delay	2.4 (0.7, 7.8)	1.2 (0.4, 3.2)	1.4 (0.7, 2.9)	1.0 (0.5, 2.3)	1.0
Learning problems	2.8 (0.9, 8.8)	1.6 (0.7, 3.7)	1.5 (0.8, 2.8)	1.0 (0.5, 2.0)	1.0
Speech problems	0.3 (0.0, 2.3)	1.9 (0.8, 4.6)	1.5 (0.7, 3.1)	1.3 (0.6, 2.8)	1.0
ADHD Medications	4.4 (1.0, 19.1)	2.9 (0.8, 10.7)	1.3 (0.4, 4.6)	1.9 (0.6, 6.3)	1.0
Psychiatric Medications	4.8 (0.8, 28.8)	1.2 (0.1, 10.8)	1.1 (0.2, 6.3)	1.3 (0.2, 7.2)	1.0
	Adjusted				
	Trouble Sleeping?				
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Attention Problems	3.5 (1.1, 11.6)	4.2 (1.6, 11.1)	2.3 (1.2, 4.7)	1.5 (0.7, 3.0)	1.0
Anxiety Problems	4.4 (1.2, 16.7)	3.9 (1.4, 11.1)	0.7 (0.2, 1.8)	0.9 (0.3, 1.2)	1.0
Behavioral Problems	1.4 (0.3, 6.4)	3.1 (1.1, 9.0)	1.6 (0.6, 3.7)	2.1 (0.8, 5.0)	1.0
Depression	6.2 (1.3, 29.8)	5.0 (1.4, 17.2)	1.5 (0.5, 4.9)	1.7 (0.5, 5.3)	1.0
Developmental Delay	3.2 (0.9, 11.7)	1.2 (0.4, 3.6)	1.6 (0.7, 3.5)	1.0 (0.9, 1.1)	1.0
Learning problems	3.8 (1.2, 12.5)	1.9 (0.8, 4.5)	1.8 (0.9, 3.5)	1.1 (0.5, 2.1)	1.0
Speech problems	0.4 (0.0, 3.2)	2.2 (0.8, 6.0)	2.0 (0.9, 4.5)	1.3 (0.6, 3.0)	1.0
ADHD Medications	13.8 (2.0, 95.2)	8.5 (1.7, 43.6)	1.7 (0.4, 7.1)	2.4 (0.6, 9.2)	1.0
Psychiatric Medications	22.0 (1.7, 286.8)	4.3 (0.3, 64.2)	0.9 (0.1, 6.7)	1.0 (0.8, 1.5)	1.0

Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates. **Bold** indicates $p < 0.05$. Trouble sleeping none of the time is the reference category.

Table S5. Association between broken out child-reported sleep disturbance and Parent-reported Child Health Questionnaire domain Z-scores in children with Fontan circulation.

	Unadjusted					
	Trouble Sleeping?					p
	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
Physical Functioning	-0.8 (-1.1, -0.2)	-0.5 (-1.5, 0.2)	-0.1 (-1.1, 0.6)	0.2 (-0.4, 0.6)	0.2 (-0.8, 0.6)	0.12
Role/Social Limits-Emotional	-0.1 (-1.2, 0.5)	0.5 (-1.8, 0.5)	0.5 (-0.1, 0.5)	0.5 (-0.6, 0.5)	0.5 (-0.6, 0.5)	0.14
Role/Social Limits- Physical	0.4 (-1.3, 0.4)	0.4 (-1.3, 0.4)	0.4 (-1.3, 0.4)	0.4 (0.0, 0.4)	0.4 (0.4, 0.4)	0.006
Bodily Pain	-0.9 (-1.4, 0.1)	0.1 (-1.4, 0.1)	0.1 (-0.9, 1.0)	0.4 (0.0, 0.4)	0.4 (0.4, 0.4)	<0.001
General Behavior	-0.2 (-1.0, 0.0)	-0.5 (-1.2, 0.0)	0.3 (-0.5, 0.6)	0.0 (-0.3, 0.6)	0.5 (-0.5, 1.1)	<0.001
Mental Health	-0.9 (-1.3, -0.2)	-0.9 (-1.6, -0.2)	-0.5 (-1.3, 0.2)	0.2 (-0.7, 0.6)	0.2 (-0.9, 0.9)	<0.001
Self Esteem	-1.4 (-1.9, -0.5)	-0.7 (-1.2, -0.2)	-0.5 (-1.2, 0.0)	-0.2 (-1.1, 0.3)	0.0 (-0.7, 0.7)	<0.001
General Health Perceptions	-0.6 (-1.4, -0.3)	-1.2 (-1.9, -0.6)	-0.4 (-1.3, 0.1)	-0.8 (-1.3, 0.1)	-0.6 (-1.2, 0)	0.02
Parental Impact-Emotional	-1.5 (-2.3, -0.7)	-1.1 (-2.3, -0.3)	-0.3 (-1.5, 0.0)	-0.3 (-1.1, 0.4)	-0.3 (-1.5, 0.4)	<0.001
Parental Impact-Time	-0.3 (-0.8, -0.3)	-0.3 (-1.4, 0.2)	0.2 (-0.3, 0.8)	-0.3 (-1.1, 0.4)	-0.3 (-1.5, 0.4)	<0.001
	Adjusted					
	Trouble Sleeping?					p
	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
Physical Functioning	-0.6 (-1.2, 0.0)	-0.7 (-1.2, -0.3)	-0.4 (-0.7, -0.1)	-0.4 (-0.7, 0.0)	-0.2 (-0.4, 0.0)	0.30
Role/Social Limits- Emotional	-0.9 (-1.6, -0.3)	-0.9 (-1.4, -0.4)	-0.4, (-0.7, 0.0)	-0.3 (-0.7, 0.1)	-0.2 (-0.5, 0.0)	0.06
Role/Social Limits- Physical	-0.5 (-1.2, 0.1)	-0.7 (-1.2, -0.2)	-0.6 (-0.9, -0.2)	-0.2 (-0.5, 0.2)	0.1 (-0.2, 0.3)	0.01
Bodily Pain	-0.9 (-1.4, -0.3)*	-0.4 (-0.8, -0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.4, 0.2)	0.5 (0.3, 0.7)	<0.001
General Behavior	-0.5 (-1.0, 0.0)	-0.5 (-0.9, -0.1)	-0.1 (-0.4, 0.1)	0.0 (-0.3, 0.3)	0.3 (0.1, 0.5)	<0.001
Mental Health	-1.0 (-1.4, -0.4)	-0.8 (-1.2, -0.4)	-0.4 (-0.7, -0.2)	-0.2 (-0.5, 0.1)	0.1 (-0.1, 0.3)	<0.001
Self Esteem	-1.3 (-1.7, -0.8)*^	-0.7 (-1.0, -0.4)	-0.7 (-0.9, -0.4)	-0.4 (-0.6, -0.1)	-0.1 (-0.3, 0.0)	<0.001
General Health Perceptions	-0.8 (-1.4, -0.2)	-1.0 (-1.5, -0.7)	-0.6 (-0.9, -0.3)	-0.7 (-1.1, -0.4)	-0.6 (-0.8, -0.4)	0.32
Parental Impact-Emotional	-1.4 (-2.0, -0.9)	-1.3 (-1.7, -0.9)	-0.9 (-1.2, -0.6)	-0.4 (-0.8, -0.1)	-0.5 (-0.7, -0.3)	0.001
Parental Impact-Time	-0.3 (-1.1, 0.4)	-0.7 (-1.2, -0.1)	-0.2 (-0.6, 0.2)	0.0 (-0.4, 0.4)	0.0 (-0.2, 0.3)	0.18

Data is presented as median (Interquartile range) for unadjusted data and mean (95% confidence interval) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis,

family income and parent level of education as covariates. For unadjusted analysis, **Bold** indicates $p < 0.05$ (Kruskal-Wallis test). For adjusted analysis, p for trend is given in the table, additional p -values are indicated by the following: **bold**, $p < 0.05$ compared to None of the time; *italics*, $p < 0.05$ compared to a little of the time; *, $p < 0.05$ compared to some of the time; ^, $p < 0.05$ compared to most of the time.

Table S6. Child-reported health-related quality of life as measured by the Congenital Heart Adolescent and Teenager questionnaire in children with Fontan circulation with broken out child-reported sleep disturbances.

	Unadjusted					
	Trouble Sleeping?					
	All of the time	Most of the time	Some of the time	A little of the time	None of the time	p
Activity Limitations	16.7 (16.7, 33.3)	10.4 (8.3, 25.0)	16.7 (4.2, 29.2)	8.3 (4.2, 16.7)	8.3 (0.0, 16.7)	<0.001
Emotional Concerns	34.4 (28.1, 40.6)	23.4 (14.1, 37.5)	21.9 (12.5, 34.4)	18.8 (6.3, 31.3)	15.6 (6.3, 25.0)	<0.001
Friendship Problems	0.0 (0.0, 0.0)	0.0 (0.0, 29.1)	0.0 (0.0, 8.3)	0.0 (0.0, 9.3)	0.0 (0.0, 0.0)	0.003
Career Concerns	30.0 (10.0, 45.0)	17.5 (7.5, 32.5)	10.0 (5.0, 32.5)	10.0 (5.0, 32.5)	5.0 (0.0, 15.0)	<0.001
Symptom Discomfort	14.0 (6.0, 20.0)	7.5 (4.5, 11.0)	6.0 (3.5, 9.0)	5.0 (2.0, 8.0)	3.0 (1.0, 6.0)	<0.001
	Adjusted					
	Trouble Sleeping?					
	All of the time	Most of the time	Some of the time	A little of the time	None of the time	p
Activity Limitations	21.2 (13.8, 28.7)	19.4 (13.8, 25.0)	21.8 (17.9, 25.8)	12.6 (8.5, 16.7)	12.0 (9.3, 14.7)	<0.001
Emotional Concerns	40.3 (32.4, 48.2)*^	28.0 (22.1, 34.0)	27.3 (23.1, 31.6)	19.6 (15.2, 24.0)	16.6 (13.8, 19.5)	<0.001
Friendship Problems	9.0 (0.1, 18.0)	17.7 (10.9, 24.5)*	9.3 (4.6, 14.0)	3.9 (-1.1, 8.9)	3.9 (0.7, 7.1)	0.006
Career Concerns	27.1 (18.4, 35.9)	24.2 (17.5, 30.9)	23.3 (18.6, 27.9)	11.7 (6.9, 16.6)	11.0 (7.8, 14.2)	<0.001
Symptom Discomfort	14.0 (11.1, 16.9)*^	9.3 (7.1, 11.5)	8.1 (6.6, 9.7)	6.0 (4.4, 7.7)	4.3 (3.3, 5.4)	<0.001

Data is presented as median (Interquartile range) for unadjusted data and mean (95% confidence interval) for adjusted data. Adjusted analysis included age, sex, pre-Fontan cardiac diagnosis, family income and parent level of education as covariates. Higher scores indicate worse quality of life. For unadjusted analysis, **Bold** indicates p<0.05 (Kruskal-Wallis test). For adjusted analysis, p for trend is given in the table, additional p-values are indicated by the following: **bold**, p<0.05 compared to None of the time; *italics*, p<0.05 compared to a little of the time; *, p<0.05 compared to some of the time; ^, p<0.05 compared to most of the time.

Table S7. Parent and Child-reported health-related quality of life in children with Fontan circulation excluding participants with reported developmental delay, use of ADHD medications or psychiatric medications.

Parent-reported health-related quality of life (Children’s Health Questionnaire Z-scores)						
	Unadjusted			Adjusted		
	Sleep Disturbance	No Sleep Disturbance	p	Sleep Disturbance	No Sleep Disturbance	p
Physical Functioning	-0.5 (-1.1, 0.2)	0.2 (-0.5, 0.6)	0.007	-0.8 (-1.1, -0.4)	-0.2 (-0.4, -0.1)	0.007
Role/Social Limits-Emotional	0.5 (-0.6, 0.5)	0.5 (-0.1, 0.5)	0.1	-0.3 (-0.6, 0.0)	-0.2 (-0.3, 0.0)	0.36
Role/Social Limits-Physical	0.4 (-0.4, 0.4)	0.4 (0.4, 0.4)	0.045	-0.5 (-0.8, -0.2)	-0.1 (-0.2, 0.1)	0.03
Bodily Pain	-0.9 (-1.6, 0.1)	0.3 (-0.4, 1.0)	<0.001	-0.8 (-1.0, -0.4)	0.2 (0.1, 0.4)	<0.001
General Behavior	-0.2 (-1.0, 0.5)	0.5 (-0.2, 1.0)	<0.001	-0.2 (-0.4, 0.1)	0.3 (0.1, 0.4)	0.01
Mental Health	-0.5 (0.2, 0.9)	0.2 (-0.5, 0.9)	<0.001	-0.5 (-0.8, -0.2)	0.1 (-0.1, 0.2)	<0.001
Self Esteem	-0.7 (-1.2, -0.2)	-0.2 (-0.9, 0.7)	0.003	-0.6 (-0.9, -0.2)	-0.3 (-0.4, -0.1)	0.09
General Health Perceptions	-1.0 (-1.6, -0.5)	-0.6 (-1.2, 0.1)	0.01	-0.9 (-1.3, -0.6)	-0.6 (-0.8, -0.4)	0.06
Parental Impact-Emotional	-0.7 (-1.9, -0.5)	0.0 (-1.1, 0.4)	<0.001	-1.1 (-1.5, -0.8)	-0.4 (-0.5, -0.2)	<0.001
Parental Impact-Time	-0.3 (-0.8, 0.5)	0.8 (-0.3, 0.8)	<0.001	-0.3 (-0.7, 0.1)	0.2 (0.0, 0.3)	0.049
Physical Summary Score	-0.5 (-1.5, 0.0)	0.1 (-0.4, 0.4)	<0.001	-0.8 (-1.1, -0.5)	-0.2 (-0.4, -0.1)	<0.001
Psychosocial Summary Score	-0.5 (-0.9, 0.0)	0.2 (-0.5, 0.8)	<0.001	-0.5 (-0.7, -0.2)	0.0 (-0.1, 0.1)	<0.005
Child-reported health-related quality of life (Congenital Heart Adolescent and Teenager Questionnaire)						
	Unadjusted			Adjusted		
	Sleep Disturbance	No Sleep Disturbance	p	Sleep Disturbance	No Sleep Disturbance	p
Activity Limitations	16.7 (8.3, 29.2)	8.3 (0.0, 16.7)	0.003	20.6 (16.2, 25.0)	13.5 (11.5, 15.5)	0.005
Emotional Concerns	28.1 (12.5, 39.1)	15.6 (6.3, 28.1)	0.001	28.7 (22.9, 34.6)	19.2 (16.5, 21.8)	0.005
Friendship Problems	0.0 (0.0, 16.7)	0.0 (0.0, 0.0)	0.01	14.5 (10.9, 18.2)	5.0 (3.3, 6.6)	<0.001
Career Concerns	20.0 (10.0, 30.0)	5.0, 0.0 (15.0)	<0.001	22.1 (18.2, 26.1)	13.0 (11.2, 14.8)	<0.001
Symptom Discomfort	7.0 (5.0, 16.5)	4.0 (2.0, 7.0)	<0.001	10.7 (8.3, 13.1)	5.5 (4.4, 6.6)	<0.001

Children with either parent or child report of sleep disturbance are included in the sleep

disturbance group. Data is presented as median (Interquartile range) for unadjusted data and

mean (95% confidence interval) for adjusted data. Adjusted analysis included age, sex, pre-

Fontan cardiac diagnosis, family income and parent level of education as covariates. **Bold** indicates $p < 0.05$.