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Understanding the Impact of Congenital Heart Disease on Behavior, Quality of Life, and Self-Perception in Adolescents

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ABSTRACT

Understanding the Impact of Congenital Heart Disease on Behavior, Quality of Life, and Self-Perception in Adolescents

By Jessica Knight

Congenital heart disease (CHD) is the most common type of birth defect. Advancements in treatment of this condition over the last several decades have dramatically improved the survival rate in these patients. However, evidence of cognitive and other developmental differences between affected children and healthy peers has raised concern over the long term impacts of this condition and its treatments. Previous literature has been limited on its assessment of these potential impacts in affected adolescents. Additionally, available studies have mostly focused on more severe forms of CHD and lacked adequate information to control for potential confounding. Therefore, the goal of this dissertation was to assess behavior, quality of life, and self-perception in a large sample of adolescents, 11-18 years old, surgically treated for CHD using siblings without a birth defect and normative samples for comparison.

Using the Child Behavior Checklist parents reported increased internalizing behavior problems, such as anxiety and depression, for their child with CHD compared with their sibling (mean difference = 4.3, 95% CI = 2.7 – 5.9). Seventeen percent of the children with CHD were reported to have clinically significant internalizing behavior problems compared with the expected 10% from population norms for this instrument. Parents also reported lower quality of life for their child with CHD compared with their siblings on all composite scores measured by the PedsQL, physical health, psychosocial health, and total quality of life. After adjusting for gender and age, the child with CHD scored 7.6 points lower on physical health (95% CI: -11.4, -3.7) and 6.8 points lower on psychosocial health (95% CI: -10.1, -3.5) than their unaffected sibling.

Adolescents' perspective of the impact of CHD was assessed using the Harter Self-Perception Profile and self-reported quality of life on the PedsQL. The adolescents with CHD generally reported normal self-esteem but lower quality of life than normative samples of healthy children. Increased severity of CHD was associated with lower perceived physical health, psychosocial health, and quality of life related to symptoms. After adjustment, other factors including household income and total number of cardiac surgeries were more strongly related to quality of life than defect severity.

The results of this dissertation suggest that those with CHD face behavioral and quality of life challenges even years after the defect has been repaired. As these differences were not only observed in those with the most severe forms of CHD, and defect severity does not appear to be the strongest influence on these outcomes, parents and clinicians should monitor all children with CHD requiring surgical intervention. Further research should utilize longitudinally collected data to better identify risk factors for these outcomes in the CHD population.

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CHAPTER 1. BACKGROUND AND SIGNIFICANCE

Congenital Heart Disease

Congenital heart disease (CHD) is the most common type of birth defect affecting almost 1% of births in the United States.[1,2] It is characterized by abnormal fetal development of the heart which impacts heart functionality and can affect blood flow throughout the body. CHD is the cause of a disproportionate amount of mortality early in life, about 4% of all neonatal deaths,[3] but survival rates are improving.[4] Because of decreased mortality from improvements in treatment and diagnosis, recent interest has shifted to long term morbidity in this population. This research is essential for reducing the impact of CHD on the children affected, their families, and the health care system.

Risk factors for CHD

For many infants born with CHD the cause is unknown. However, about 15% are associated with a recognized chromosomal abnormality or syndrome.[5] The most common anomaly among children with CHD is trisomy 21 which also causes Down syndrome. It is highly associated with atrial septal defects. Others include 22q11 deletion syndrome, Alagille syndrome, Noonan syndrome, CHARGE, Marfan syndrome, and Williams syndrome among others.[6] Children whose CHD is related to genetic causes are often considered separately from other children with CHD because of the presence of co-occurring conditions related to the syndrome that further affect the child's morbidity and mortality.

The majority of CHD cases are not linked to known genetic causes and even associated genes may be modified by the environment. Therefore, research is ongoing to find modifiable, environmental risk factors for this condition. Because the major

structures of the heart are formed by eight weeks gestation, any exposures later in pregnancy cannot be the cause of the heart abnormalities. Thus, the window of relevant exposure is before pregnancy or early in pregnancy.

In 2006, the American Heart Association (AHA) published a review of current literature on parental exposures during the periconception period (three months before pregnancy) and the first trimester. This review identified one factor generally associated with decreased risk of CHD: periconception use of a multivitamin containing folic acid. Maternal factors associated with a definite or possible increased risk for CHD include untreated phenylketonuria; pregestational diabetes; rubella, frebrile illness, or influenza during the first trimester; epilepsy (it is unclear whether maternal seizures are an independent risk factor or it is the medication to treat them); use of certain medications including vitamin A, anticonvulsants, Ibuprofen, sulfasalazine, thalidomide, and trimethoprim-sulfonamide; marijuana; and organic solvents.[7] A more recent review added hypercholesterolemia, hyperhomocysteinemia, hypertension, prepregnancy obesity, experience of stress, cigarette smoking, and several more medications to this list.[8]

Non-Hispanic blacks have been found to have a significantly lower prevalence of CHD at birth than non-Hispanic Whites (prevalence ratio: 0.42; 95% CI: 0.35 – 0.49), and this difference appears to be widening over time.[9] A large study in Denmark demonstrated an association between low maternal and paternal socio-occupational status and having an infant with CHD.[10] Another study in the US using the NBDPS database did not find a statistically significant association between composite socioeconomic status and CHD, but unemployed parents and low parental education were associated

with increased risk.[11] Older maternal age is also related to increased prevalence of several types of CHD. Female infants are more likely to have septal defects, but males are more likely to be born with tetralogy of Fallot, transposition of the great arteries, and total anomalous pulmonary venous return. As this suggests, male infants are more likely to have severe CHD and receive corrective surgery.[2,12]

Types of CHD

The term CHD includes a number of heterogeneous diagnoses. The severity of the defect depends on the structures involved and the degree to which blood flow is impacted. The most severe forms of CHD are called Critical Congenital Heart Defects which comprise of approximately 25% of CHD cases.[4] These often cause low levels of oxygen in the blood leading to cyanosis, and all require surgical repair within the first year of life for the infant to survive. Critical CHDs include Coartaction of the aorta, double-outlet right ventricle, transposition of the great arteries, Ebstein anomaly, hypoplastic left heart syndrome, interrupted aortic arch, pulmonary atresia, single ventricle, total anomalous pulmonary venous return, Tetralogy of Fallot, tricuspid atresia, and truncus arteriousus.[13] Other forms of CHD that are less severe may still require some sort of treatment to restore normal function to the heart. The most common among these are ventricular septal defects (VSD) and atrial septal defects (ASD).[2,14]

Symptoms of CHD

Some of the effects of CHD and symptoms are inherently tied to the type of defect. Mild forms of CHD, especially septal defects, may result in no evident symptoms or only an asymptomatic heart murmur. However, many forms require treatment early in life for survival. Infants with CHD may present with blue-tinted nails or lips, fast or

difficulty breathing, tiredness with feeding, or sleepiness. These outward signs are indications of low blood oxygen levels and the heart exerting extra energy to maintain circulation. Older children with CHD may tire easily or become short of breath during physical activity. Severe defects can eventually lead to the accumulation of blood and fluid in the lungs and/or heart failure. [14,15]

The natural fetal blood circulation includes two openings in the heart that shunt blood from the right to the left side of the heart in utero. This allows most of the blood to bypass the lungs while oxygen is being obtained from the placenta. Once born, vascular resistance decreases in the infant's lungs and blood circulation begins to follow the normal path. Within a few days of birth the ductus arteriousus and foramen ovale will close. Until they do, some blood is still allowed to flow between the right and left sides of the heart. In infants with CHD this can often mask a serious problem. Essentially, the two openings may help compensate for abnormal blood flow caused by the CHD, but when these close, blood may be blocked from normal circulation. Therefore, some children with critical congenital heart defects may appear to be of good health in the hospital, but can experience large drops in blood oxygen levels and quickly begin to show symptoms at home once these openings close. This can be dangerous for the infant if they experience severe hypoxia, and they likely will require immediate medical attention. Newborn screening has recently been instituted to identify children with low blood-oxygen levels before discharge in the hospital. This consists of measurements of blood-oxygen taken by a pulse-oximetry device in the hospital to identify levels of oxygen below normal and/or discrepancies in oxygen-levels in different parts of the

body. Therefore, this screening is mostly targeted toward critical CHD but may identify other types of heart defects as well.[13,16]

Treatment and management of CHD

Some forms of CHD can be identified prenatally through ultrasound or a fetal echocardiogram. However, approximately 90% of CHD are diagnosed after birth.[17] Over the past two decades there have been vast improvements in surgeries to treat CHD which has dramatically increased the likelihood of survival for infants born with this condition. Survival rates for the first year of life are currently 97% in infants born with isolated non-critical CHD and 75% in infants with critical CHD. Mortality then tapers and survival to the age of 18 is 95% for non-critical CHD and 69% for critical CHD.[4]

Treatment of CHD is dependent on the type and severity of the defect. Small septal defects often require no intervention and may close on their own. However, large holes must be patched. Repairs using a catheter can be performed on ASDs and some VSDs. However, open-heart surgery is more often performed to patch large VSDs. Catheterization is often less stressful on the body than open-heart surgery, but can have its own complications. Other treatments may be necessary to control symptoms before and after surgery including anticongestive therapy for those who begin to show signs of congestive heart failure, high calorie formula, and prophylaxis against respiratory syncytial virus.[14,15]

In obstructive anomalies blood flow is restricted in a certain area of the heart or major blood vessels near the heart. This can occur because of narrowing (stenosis) of one of the four valves throughout the heart or in the pulmonary artery or aorta. Similar to septal defects, some obstructive defects may not require treatment if the narrowing or

blockage is mild. When necessary, catheterization can be used to open narrowed valves such as in pulmonary stenosis. In this procedure a balloon on the end of the catheter is inflated within the valve to push apart the valve leaflets. In other cases, surgery may be necessary to replace the problematic valve. Catheterization has been used in some cases of coartation of the aorta, but most patients require surgical resection of the narrowed section and reconnection of the two ends.[14,15,18]

Critical CHDs are more complex and open-heart surgery is required in infancy. Some blockage defects, such as tricuspid atresia, are treated by creating a shunt for blood to flow through the previously impeded area. Other defects require a series of surgical repairs to restore blood flow. For example, hypoplastic left heart syndrome (HLHS) is usually treated with a series of three surgeries including the Norwood procedure conducted soon after birth, a bidirectional Glenn or hemi-Fontan is performed at 4-6 months of age, and the Fontan procedure between 18 months and 4 years of age. Some infants with HLHS and other complex defects undergo a heart transplant instead. All children with cyanotic defects may need medication for the rest of their lives to manage symptoms and should be followed closely by a pediatric cardiologist.[14,15,18]

Neurocognitive deficits and CHD

Biologic mechanisms that possibly impact cognition in children with CHD

Long-term neurodevelopmental outcomes in children with CHD are of elevated concern. CHD can begin to affect brain growth and development in utero through altered cerebral blood flow and impaired oxygen delivery.[19] This is supported by evidence of less mature brain development at birth in some infants with complex CHD. One study

using magnetic resonance imaging (MRI) found that full-term infants with CHD had an average brain maturation comparable to that of a healthy infant at 35 weeks gestation.[20] Another sign of cognitive growth restriction in utero is the increased prevalence of microcephaly which has been found in 8-33% of infants with CHD.[21-24] This delayed growth continues in infancy when brain maturation and myelination are at an essential stage and especially sensitive to changes in blood flow.[20,21] Extended periods of hypoxia may be experienced before surgical repair, and may even persist after surgery in certain children damaging brain development.[25]

As children with CHD are already at an increased risk for delayed maturation at birth, premature infants with CHD have an additional risk for neurodevelopmental delay. This increased risk has been suggested to occur in infants born as old as 38 weeks gestation compare to those carried to full term.[26] This is of particular importance for the CHD population as infants with CHD are more likely to be born preterm.[27]

Delayed cognitive growth may be compounded by surgery which presents another set of risks for brain injury. Open-heart surgery requires cardiopulmonary bypass or deep hypothermic circulatory arrest (DHCA) to support the vital organs. However, these can cause microemoboli or global cerebral ischemia which can lead to ischemic stroke and increased periventricular leukomalacia.[28] For example, periventricular leukomalacia has been shown to be present in 16% of patients before surgery and increase to 48% after surgery.[29] Patients placed on mechanical support including extracorporeal membrane oxygenation and ventricular assist device, are at risk for thromboembolism and/or hemorrhage.[30,31] Cardiopulmonary resuscitation results in a period of hypoxia which can lead to permanent damage.[32,33] Both open-heart surgery and catheterization require early

life exposure to anesthesia which has been implicated in cognitive differences later in life.[34] Finally, prolonged hospitalization after surgery has been associated with poorer cognitive outcomes. This association remains after adjustment for demographic and perioperative characteristics suggesting that it is not simply a proxy of the severity of the defect or the complexity of the surgery.[35]

Postoperative seizures may also cause permanent brain injury which can affect later outcomes.[36] Seizures appear to occur more frequently in children exposed to DHCA compared to low-flow cardiopulmonary bypass, and the incidence of seizures depends on whether the researchers identify only those that are clinically evident or use electroencephalography (EEG) to identify subclinical seizures as well. One study found clinical seizures in 11.5% of infants with DHCA and 1.2% of those with low-flow CPB within the first seven days after surgery. Forty-eight hour review using electroencephalography revealed that, in fact, 25.7% of those with DHCA and 12.9% of those with CPB experienced seizure activity.[37] Another study has suggested that timely identification of seizure activity and use of treatment measures, even when subclinical, may prevent permanent damage from such events.[38]

Cognitive outcomes in children and adolescents with CHD

In accordance with the risk of neurologic changes and injury, current studies have shown growing evidence that children with CHD on average score in the normal range but significantly lower than the general population on cognitive tests. Furthermore, among children with high risk lesions, the prevalence of intellectual disability (IQ < 70) has been much higher than expected.[28] For example, cognitive evaluation of 28 children with hypoplastic left heart syndrome revealed a median full scale IQ of 86 and 18% of

patients scored below 70.[39] In another study, children with tetralogy of Fallot and ventricular septal defect (VSD) had a mean IQ of 92.2. Those with VSD had slightly higher scores than those with tetralogy of Fallot (mean IQ: 93.1 and 91.4 respectively) but this difference was not significant.[40]

Specific areas of impairment that have been found in children with CHD include motor function, visual-motor coordination, working memory, and language skills.[40-42] In the same study described above of children with tetralogy of Fallot and VSD, in addition to IQ, motor function, receptive language, expressive language, and acquired abilities were measured. While all mean sub scores were below normal, the lowest scores were found on the motor quotient (mean = 86.2), and there was a significant difference between the motor function of the tetralogy of Fallot and the VSD groups (mean = 80.4 and 91.6 respectively) suggesting that there is variation in cognitive injury by defect.[40] Similarly, a study of children with total anomalous pulmonary venous connection showed the largest deficit to exist in motor and visual-motor function.[41]

Which clinical factors are most associated with long term cognition is still uncertain. The Boston Circulatory Arrest Trial randomized 171 patients with dextrotransposition of the great arteries to receive the arterial switch operation under total circulatory arrest or low-flow cardiopulmonary bypass. At eight years of age, the groups did not differ in IQ, but children who experienced total circulatory arrest performed worse on tests of motor function.[42] At 16 years old, those treated with circulatory arrest experienced worse visual-spatial and executive function. The most consistent finding was the association of postoperative seizures with poorer outcomes which were more common in those who received circulatory arrest.[43] Other studies have found mixed

results for the associations between neurodevelopment and cumulative duration of circulatory arrest, length of stay in the ICU, low birth weight, post-operative seizures, prenatal diagnosis and other clinical features.[40,44-47]

Academics

Despite children with CHD having cognitive scores below normal on average, parents of these children mostly report their child performing at or above average in school.[39] However, results from teachers' ratings of children with CHD show a higher percent performing below average, suggesting that parents are optimistic about their child's scholastic performance.[48] Children with CHD are also reported to have higher than expected rates of receipt of special education services, and such services have been reported for the majority of children with certain high-risk lesions.[43,49] In a group of 109 five to ten year olds with a surgically repaired complex heart defect, 49% were receiving remedial academic services and 15% were placed in a special education classroom.[48]

Behavior

Structural changes in the brain that affect cognition may also affect the behavior of children with CHD. Furthermore, behavior has been shown to differ in children with other chronic conditions compared to healthy children in total, externalizing, and internalizing behavior scores.[50] Externalizing behaviors are more outward acts including delinquent and aggressive behavior, whereas, internalizing behaviors include somatic complaints, anxiety, depression, and social withdrawal. In children with chronic conditions, externalizing behavioral problems may stem from physical changes in the brain that affect behavior regulation or from frustration related to the illness.

Alternatively, internalizing behaviors in these children can be increased from a perceived lack of control over the condition and its effects, fear of symptoms or treatments, restriction of positive activities, peer rejection, pain, and side effects of therapy.[50]

Among the CHD population results of behavioral assessments have varied. One study of children with various forms of CHD found that boys with the condition had significantly more total and internalizing behavior problems compared with healthy boys. Girls with CHD also were reported to have significantly more internalizing problems than healthy girls. Furthermore, among girls, those with functional single ventricle defects had the highest scores for total and internalizing behavior problems.[51] However, another study of children who had undergone the Fontan operation, which includes those with HLHS and other forms of functional single ventricle, found that all but one child out of 51 had behavior scores in the normal range.[52] Both studies assessed behavior using the Child Behavior Checklist (CBCL), and therefore at first it is unclear why this difference in results is observed. This is especially true because the study which found mostly normal scores included children with more severe forms of CHD. One contributing factor may be the differences in age between the studies because the population in which differences were observed was11-16 years old, whereas the average age in the other study was about five years old.

A meta-analysis was conducted of articles on behavior in children with CHD published between 1980 and 2005 to resolve these discrepancies. It in fact agreed with the pattern seen in the articles previously described and found that only older children with CHD (mean study age > 10 years old) had an increased risk for total and internalizing behavior problems. It also found a small increased risk for externalizing

behavior problems in older children.[53] Unfortunately, the meta-analysis contained only two studies with populations whose mean age was greater than 11 years old, and both were older studies whose participants were treated under outdated practices.[54,55] Therefore, from this it was still unclear how behavior was impacted in adolescents with CHD.

Studies published since the meta-analysis have also found differences in behavior for children with CHD. One such study of 232 three year olds who had a single ventricle defect collected information from parents on the Behavior Assessment System for Children. Compared to a normative sample, the children with CHD had increased somatization scores but actually had lower scores in aggression, depression, atypicality, and withdrawn behavior.[56] In another study of children ages 7-17 with various types of CHD, parents reported on the CBCL that overall 17% had total behavior scores high enough to be clinically relevant. This was significantly higher than the 10% of clinically relevant scores in the reference population. However, separating the boys and girls, only boys were significantly higher than the referent group (21% for boys and 12% for girls above the clinical cutoff). Interestingly, when the groups were separated into age categories of 7-12 and 13-17, the total behavior scores were slightly higher for the 7-12 year old group. Parents reported significantly higher scores for the children with CHD on somatic complaints, social problems, attention problems, and internalizing problems. In this study, children 11 and older were asked to complete the Youth Self-Report assessment. No increased problems were reported by either gender or age group, and rule-breaking behavior was decreased in the CHD group compared to the reference group. However, when self- and parent-report were compared within the same child,

children reported significantly more withdrawn/ depressed, social problems, attention problems, and total problems than their parents.[57]

Another study of 318 children with a range of CHD diagnoses, 11-16 years old, found that patients self-reported more behavior problems than were reported by parents on almost every scale including total, internalizing, and externalizing problems. However, compared to the healthy group, boys only self-reported more somatic complaints and reported less withdrawn and delinquent behaviors. There were no categories in which girls self-reported more problems than the healthy controls and reported less total, internalizing, externalizing, withdrawn, anxious/depression, attention, delinquent, and aggressive behaviors.[58] The patterns that emerge from these studies of children with CHD include increased risk for somatic problems, higher levels of behavioral problems in males, and children with CHD reporting similar behavioral problems compared to their healthy peers but more problems than their reported by their parents. Furthermore, there are suggestions that total and internalizing behaviors may be increased in children with CHD, but these results have been less consistent.

In the Boston Circulatory Arrest Trial, behavior was measured by the parents at ages four and eight using the CBCL and also by their teachers at age eight. This allows for the longitudinal evaluation of behavioral change in the same children. The researchers found that from four to eight years of age, scores generally increased indicating the development of worse behavior with older age. At eight years old, parents rated boys with CHD worse than the general population in somatic complaints and attention problems, but reported less withdrawn and externalizing behaviors. Girls were also reported by parents to have increased somatic complaints compared to the population

mean and were no different in the other categories. Parents reported that among the girls and boys combined, 19% had total behavior scores high enough to be of clinical concern (9% had somatic complaint scores in the clinical concern range). The teacher report indicated that boys had significantly more social, thought, and attention problems than the general population. According to the teachers, girls with CHD had less delinquent behavior than the general population and were similar in all other areas. The teacher report indicated that 22% of the study cohort scored high enough on total behavior problems to be of clinical concern. It is important to note that about 75% of the population was male so this group had more power to detect differences in scores and there were 155 children in the study.[59]

As the previous studies have indicated, behavior scores have been found to vary by the relationship that the individual assessing behavior has with the child with CHD. In general, children with CHD tend to report more problems than parents.[57,58] It has been suggested that children with CHD deal with their problems internally and are therefore aware of their limitations, but do not make these evident to their parents. Another hypothesis is that because parents are well aware of these children's physical limitations that they do not want to recognize deficits in other areas of life. This is in line with the perception that parents of children with CHD may be overprotective in general.[58]

A problem area that has been indicated in a number of studies is attention, and this has motivated other studies to focus on this area and the prevalence of Attention Deficit Disorder/ Attention Deficit Hyperactivity Disorder (ADD/ADHD) in children with CHD. An analysis of 109 children from the Allopurinol Neurocardiac Protection Trial cohort at 5-10 years old found that the number of children with CHD receiving high-risk scores for

inattention and hyperactivity was three to four times higher than in the general population. Specifically, on the Behavior Assessment System for Children, parents reported 11% of the children with CHD as high-risk for inattention and 10% for hyperactivity. Teachers scored 8% of children in the high-risk range for inattention and hyperactivity. On the ADHD-IV scales, also completed by parents and teachers, 5% of children with CHD would be highly likely to have ADHD and another 15% would be at risk for an ADHD diagnosis.[48] Another study compared scores on an ADHD screening tool between children with CHD to a comparison group from the same population, instead of relying on population standards. This study found that 29% of children who had experienced open heart surgery scored positive on the screener compared to only 3% in the control group.[60]

Finally, depression and anxiety are often considered in instruments of behavior. In one study of adolescents with heart problems, 3% were reported to have probable depression and 6% possible depression using the Hospital Anxiety and Depression Scale. Additionally, ten percent scored in the range of probable anxiety and another 17% with possible anxiety.[61] Another study that compared adults with CHD to sex and age matched controls found more anxiety among the CHD group (average scores for CHD group: 9.22 vs. healthy group: 8.11) but no difference in rates of depression (average score for CHD group: 6.51 vs. healthy group: 6.36). After control of demographic characteristics and social support, no association remained between CHD and anxiety or depression.[62] Other estimates of depression in the CHD population have ranged from 40 to over 50% with at least mild symptoms.[62,63]

Factors associated with behavior within the CHD population

Several studies have examined treatment and patient characteristics among children with CHD that are associated with increased behavior problems. One early study assessed the predictive ability of patient age and gender, medical history, characteristics of heart surgery, complications after surgery, number of heart operations, and the presence of intellectual disability or other physical problems. In their final model, higher total behavior problems were predicted by the number of heart operations and the use of deep hypothermic circulatory arrest and internalizing problems were predicted by the number of heart operations, deep hypothermia, younger gestational age, low systemic oxygen saturation, and older age at surgical repair. Externalizing problems were predicted by a greater number of heart operations. In this study, the diagnostic group of the child was not significantly associated with behavior.[64]

In another group of children with surgically corrected transposition of the great arteries, features of surgery and health of the patient also predicted behavior. Here, severe preoperative hypoxia was associated with social problems and social involvement, longer duration of deep hypothermic circulatory arrest was associated with social involvement, the presence of perioperative and postoperative cardiocirculatory insufficiency predicted internalizing, externalizing, attention, and total problems. This study also evaluated the predictive ability of earlier neurodevelopmental assessments and found that reduced expressive language was a predictor of total behavioral problems.[65]

In contrast, one study of four diagnostic groups of CHD did find differences in the scores on the CBCL for social and externalizing behavior problems by type of defect. The children with ventricular septal defects had the highest reported scores, more behavior problems, for both problem areas followed by transposition of the great arteries.

Children with atrial septal defects or pulmonary stenosis had similar levels of social and externalizing problems and they were the lowest among the children with CHD. Nevertheless, there were no significant difference by diagnostic group on the Youth Self-Report measure which could be because less children than parents responded, but the pattern was not the same either. This study only controlled for age and sex but no other treatment features which could be driving the appearance of differences by diagnostic group.[57]

One exposure mentioned in several studies above is deep hypothermic circulatory arrest. The Boston Circulatory Arrest Trial found almost no behavioral differences between those treated with low-flow bypass compared to circulatory arrest, although the few differences found actually suggested worse behavioral outcomes in those with low-flow bypass. This is in contrast to cognition which was lower in those with circulatory arrest. Seizures experienced after surgery were associated with social and attention problems.[59] This finding is partially supported by another group which measured seizure activity for the first 48 hours after surgery using an EEG. This group found that patients who experienced seizures were more likely to report impaired social interactions/ restricted behavior but were no different in regards to attention and impulsivity at ages 4-5.[38] Another study found increased attention problems to be associated with younger gestational age.[66]

A number of studies have also investigated the association between maternal and familial characteristics and childhood behavior. It has been shown that having a child with CHD increases maternal and familial stress and that the risk of stress is higher for parents of children with severe CHD, as would be expected.[67] One study found that

parental ratings on the Parenting Stress Index at age four were significantly associated with parent-reported behavior at age eight. Some teacher-reported behaviors at eight years old were also associated with parent reported stress at age four.[59] This suggests that the increases in behavior problems by parent report are not simply a reflection of the parent's perception of increased problems. From this evidence it is still unclear whether the behavior problems were present before the age of four which led to maternal stress, whether increased maternal stress can lead to increased behavioral problems in the child, or maternal stress and child behavior are similarly affected by other factors. One study has suggested that maternal stress and child behavioral problems are mutually influential. In this study, child internalizing behavior at 18 months was associated with maternal stress at 36 months, and maternal stress at 18 months was associated with child behavior at 36 months. However, this pattern could also be due to other factors influencing both. This trend was true for the healthy population and families with a child with CHD. What is different in families with CHD is that the child and mother are at higher risk for these behaviors and stress.[67] Another study found lower perceived social support to be related to anxiety and depression in adults with CHD. Additionally, somatic symptoms and perceived financial strain were associated with anxiety and depression.[62]

Exercise has been proposed as a mediator to improve behavioral outcomes in adolescents with CHD. Several non-randomized trials initially showed positive results of exercise intervention programs improving parent-reported emotional, behavioral, and physical functioning. This led to a trial conducted from 2010 to 2012 that randomized 71 adolescents with tetralogy of Fallot or a Fontan circulation to participate in a 12 week exercise program or receive no intervention. Behavior was measured at baseline and

after 12 weeks by parent- and child-report. No effect of the exercise program was observed.[68] Although the randomized trial provides evidence against the power of exercise to alter behavior, it may be that 12 weeks is not a long enough period to change behavior.

A final factor investigated in relationship to behavior is Apolipoprotein E (APOE) gene. APOE is a regulator of cholesterol metabolism and is involved in outcomes after central nervous system injury. A prospective cohort study of infants who underwent surgery to treat a CHD has examined the effect of certain alleles of the APOE gene on behavior at four years old. Adjusting for other covariates, one specific allele of APOE was associated with increased scores on somatic complaints, pervasive developmental problems, and internalizing problems. This suggests that this gene may in fact mediate the association between CHD and behavior.[69]

Research limitations and gaps

The research summarized above suggests that children with CHD are at an increased risk for behavioral problems at older ages. Somatic complaints, attention problems, and internalizing behavior problems are especially reported at an increased rate in this population. However, the studies described above mostly had small sample sizes and relied on normative data for comparison. Many of these studies have not controlled for important confounders such as SES and have used predictive models to assess the relationships between pre-, peri-, and post-operative features and behavior later in life. Although there is value in determining predictive factors, a causal interpretation is necessary to target certain treatments for intervention.

Research has demonstrated that behavioral problems increase with age, but many studies that assess factors related to behavior have been conducted in younger children. This may be problematic if behavior problems are not as well identified in children with CHD at these younger ages. The exception to this is the exercise trial conducted in adolescents that proved to have null results (however, the trial was only 12 weeks which may not be sufficient time to alter behavior). Maternal and familial stress do seem to play a role in child behavior and may need to be considered, especially when behavior is measured from parent-report.

Therefore, more research is needed to confirm behavioral patterns in older children and determine which treatment factors are related to increased problems at this age. Larger samples are needed to ensure that adequate power is available, especially to observe differences in subgroups. Causal models should be employed that include potential confounders such as demographics and familial characteristics. To allow for such adjustment, comparison groups should be recruited from the same source population.

Self-perception

Self-perception is considered a multidimensional framework because it is recognized that people think of themselves differently across areas of life. These domains in childhood and adolescence include scholastic competence, social competence, athletic competence, physical appearance, and behavioral conduct. However, global self-worth, or overall self-esteem, is also an important measure and is different than simply the sum of the separate domains.[70] Self-esteem has been found to be lower in children with chronic illnesses,[71] and self-perception is affected in children who have other

chronic health problems such as being overweight.[72] This is an important measure because it has been shown to be associated with depression, anxiety, and eating disorders in healthy adolescents.[73] Therefore, self-perception may also be an important component in the long term effects of CHD, but thus far research has been sparse in this area.

One study of children with CHD did not find a difference in self-perception from healthy controls despite demonstrating more school, behavioral, and depressive problems. However, only 23 children completed the self-perception scale, whereas parents of 43 children completed the other questionnaires. Furthermore, there was a trend of lower scores for the children with CHD, particularly on the scales for scholar competence, social acceptance, athletic skills and self-worth.[74] These are reasonable considering the children had increased parent-report of school difficulties and social behavior problems, and children with CHD are sometimes less physically active even when not clinically recommended.

An older study of children with CHD undergoing cardiac surgery compared self-perception before and after surgery with children receiving bone marrow transplant and healthy children. Before surgery, children with CHD considered themselves to be weaker but less angry than the children receiving bone marrow transplant and weaker, more frightened, and more ill than the healthy children. The total self-perception score was also significantly lower for the CHD group compared to the healthy group. However, the ideal self was not different between the three groups. After surgery, children with CHD rated themselves similarly to the healthy group and only more frightened compared to the bone marrow transplant group. As this implies, children with CHD had higher self-perception scores after surgery.[75] The findings after surgery appear to be in concordance

with the study above. This makes sense because in the more current study, most, if not all, of the children with CHD would have completed their surgical treatments before assessment of self-perception.

Other studies in this area have shown mixed results. Only a difference in self-perceived physical self-concept was observed between 9-12 year olds with CHD and a healthy comparison group.[76] Another investigation found lower self-concept among males with CHD as compared to healthy boys. In this study, girls with CHD were no different than healthy females the same age.[77] Despite this limited information on self-perception in children with CHD, lower global self-worth was found to be associated with lower self-reported quality of life and more self-reported internalizing and externalizing behaviors after controlling for other factors.[78]

Research limitations and gaps

The current literature on self-perception in patients with CHD is limited and the studies that are available have small sample sizes, use different instruments that are not always validated, and have not controlled for other factors that may affect self-perception. There is evidence that children with CHD may be more insecure and fearful before treatment is completed. However, in modern treatment, surgery is typically completed before school entry and self-concept cannot be reliably obtained from the patients at these young ages. It also may be that subgroups within the CHD population are at a higher risk of low self-esteem, but further research is needed to examine this. Despite the incomplete of evidence, there is a need to understand self-perception in children with CHD because it may enhance the understanding of other self-reported measures of this population.

Quality of life

Health-related quality of life encompasses the perceived impacts of disease and treatment on physical, mental, and social domains of the individual's life. The importance of assessing quality of life in children with chronic conditions, instead of the simply their physical health, has been increasingly recognized. Therefore, a number of generic and disease specific validated instruments have been created to assess these impacts in the pediatric population including the TNO-AZL Children's Quality of Life (TACQOL), Child Health Questionnaire (CHQ) and Pediatric Quality of Life Inventory (PedsQL).[79] Studies using these instruments have shown that children with chronic illnesses generally have poorer quality of life compared to healthy children.

A large study used the PedsQL to compare quality of life between groups of children with various chronic illnesses including a group with cardiac conditions. From child self-report, the healthy group had the highest score compared to the children with a chronic condition on total quality of life and each separate domain. In general, children with cerebral palsy had the lowest scores followed by those with a rheumatologic condition. Cancer, psychiatric disorders, obesity, end stage renal disease, and asthma had scores in between the lowest groups and the healthy children. Children with cardiac problems, gastrointestinal conditions, and diabetes were closest to the healthy controls, but the cardiac goup, which included CHD and other conditions, had significantly and meaningfully lower total scores, physical health, social functioning and school functioning compared with the healthy group. Parent-reported scores revealed a similar pattern, but children in the cardiac group were significantly different from the healthy

group in psychosocial health, emotional functioning, and school functioning. The severity of the cardiac condition was inversely associated with quality of life scores.[80]

A recent study of 1,138 patients with CHD from seven centers across the US measured quality of life using child- and parent report of the PedsQL. All patients were 8-18 years old, were recruited while visiting an outpatient cardiac clinic, and did not have a known developmental delay or major comorbid medical condition. In addition to a healthy group, this study also included children with other chronic conditions to be used for comparison. According to patient and parent report, children with CHD scored significantly lower than the healthy children on every comparison (8-12 year olds, patient-report total mean scores: 75.8 vs. 86.2; 8-12 year olds, parent-report total mean scores: 74.7 vs. 84.9; 13-18 year olds, patient-report total mean scores: 79.0 vs. 86.9; 13-18 year olds, parent-report total mean scores: 74.2 vs. 85.0). Children with CHD reported similar scores to the children with other chronic conditions which included end stage renal disease, asthma, obesity, and diabetes. The parents of children with CHD also reported similar scores to the other groups with chronic conditions, except they reported higher quality of life compared to the asthma group. For all comparisons except emotional function, children with mild CHD (no surgical repair) had better quality of life scores than other children with CHD, and children with surgically repaired biventricular CHD had higher quality of life scores compared to those with single ventricular CHD.[81]

Schaefer et al. did not find differences in patient-reported health-related quality of life of adolescents with CHD compared to population norms, but parents reported significantly more peer relationship and total problems. This study included only 59 children with CHD and therefore power may have been an issue.[82] Another study of 154

children 8-15 years old with atrial septal defects, ventricular septal defects, transposition of the great arteries, or pulmonary stenosis found significantly lower scores for this group compared to normative data on motor, cognitive, and positive emotional functioning. When this sample was divided into those 8-11 and 12-15, younger children had lower scores than norms on motor, autonomy, cognitive, social, and positive emotional functioning, whereas older children only scored lower on motor functioning. No differences were found on scores between the four diagnostic groups.[57]

Recent cardiac specific measures of quality of life have been created to assess areas of specific concern in this group. One study used the PedsQL cardiac module to compare children with hypoplastic left heart syndrome to those with tetralogy of Fallot. Child-report on the generic PedsQL indicated lower quality of life in the HLHS group, but no differences were found on the cardiac module scores. Parents of children with HLHS reported lower symptom scores and higher cognitive problems and perceived treatment anxiety compared to parents of children with TOF.[83] Among a group of patients with transposition of the great arteries, parents of those with anatomic repair compared with conventional or no repair reported less residual heart disease, appearance problems, and treatment anxiety.[84]

Factors associated with quality of life within the CHD population

Factors that have been associated with quality of life among children with CHD include SES, especially family income,[85] the presence of a chromosomal abnormality,[86] social disadvantage,[87] a sense of coherence, and physical health.[88] These factors suggest that family characteristics are important for understanding quality of life. Family income was associated with total quality of life score even after controlling for sex, race,

diagnosis, and whether the defect required no repair, was surgically repaired, or a heart transplant was needed. In this model, family income explained 4-5% of the variation in patient- and parent-reported scores.[85] The study on social disadvantage defined this characteristic as a sum of factors including a single-parent household, being of ethnic minority, unfinished parental education, unfinished parental professional training, and/or parental unemployment. In addition to social disadvantage being related to lower quality of life, this study found significant interaction between social disadvantage and disease severity which increased the negative impact on children with CHD.[87] Sense of coherence is characterized by enhanced feelings of comprehensibility, manageability, and meaningfulness which has been suggested to be higher in children with chronic illnesses compared to healthy children.[89] In children with CHD, social coherence has been associated with increased quality of life after adjustment for education level, romantic relationships, perceived health status, health risk behavior, and depressive symptoms.[88] Another study found that sense of coherence was also related to disease-specific aspects of quality of life including symptoms, physical appearance, and cognitive problems.[90]

As with behavior, physical activity has been of particular interest in its association with quality of life. The American Heart Association states that most children with CHD should not be limited in their physical activity and would benefit from regular exercise.[91] Therefore, it is recommended that most children with CHD follow the recommended exercise levels for healthy children and many can participate in sports with no restrictions. However, patients with complex CHD should talk to their doctor, and especially those with ventricular dysfunction and a high risk for arrhythmia should take additional precautions.[92,93] In one study, subjective and objective measures of physical

activity were shown to be within normal range for children with corrected tetralogy of fallot and ventricular septal defects. All children were reported to participate in school sports and over half reported participation in leisure sports. During a treadmill exercise test, all patients remained asymptomatic and were able to push themselves to the limit. However, endurance times were slightly shorter for children with TOF compared to the VSD group and healthy controls. Time exposed to cardiopulmonary bypass was correlated with parent-perceived functional status (New York Heart Association class), and endurance was associated with duration of mechanical ventilation and SES.[40]

Similarly to the increased prevalence of obesity in the general population, studies have shown alarming rates of high BMI in the CHD population. A study of 1,523 children with heart disease found that 24% of patients with biventricular repair and 16% of Fontan patients were obese or overweight. This was less than the 31% reported as the national prevalence of obese and overweight children 6-19 years old. However, excess weight may be more important in children with CHD because of the increased risk for adverse cardiovascular effects.[94] Furthermore, activity levels in adults with CHD are well below recommendations and tend to decrease with severity of CHD. In one study population, only 23% of adults with the mildest forms of CHD met the national activity recommendations and no patients in the most severe group met these.[95]

One study of quality of life, health status, and depression in adolescents and adults with a single functional ventricle after undergoing the Fontan operation found overall decreased health status and increased depression compared to health controls. Physical function and bodily pain were also worse in the CHD group. The average self-reported quality of life score was not different from the normal population but, functional status,

depression, and social support accounted for over half of the variation in the quality of life. None of the demographic characteristics included were significantly associated with quality of life.[63]

Research limitations and gaps

Compared with behavior and self-perception, quality of life has benefited from several larger studies in children with heart problems. However, many studies of this outcome have included quite heterogeneous groups that include children who required no treatment for their heart defect to those with single ventricle. Quality of life tended to be related to defect severity, but many studies did not consider characteristics of treatment. Therefore, more research is necessary to describe quality of life in children with CHD who require surgical intervention, and determine whether it varies by severity of defect or whether these differences can be attributed to aspects of treatment. Other important demographic and familial characteristics should also be included to reduce confounding in the comparisons between children with CHD and the healthy population. Additionally, several cardiac specific instruments have recently been developed and more research is needed to understand how children with CHD rate on these.

As noted throughout the results above, quality of life can be measured through parent- or patient-report, and although both are valid measures they often yield different results. In the general literature, parents of healthy children tend to report higher quality of life than the children themselves. However, children with health conditions tend to report higher quality of life than their parents.[96] It has been suggested in a healthy group of children that parent and child responses differ because of different reasoning and response styles, but that the questions are interpreted similarly.[97] It is unclear whether

this would also be true for the CHD population and how these differences should be interpreted.

Summary

Behavior, self-perception, and quality of life are important aspects of life in all children and may be more important among children with CHD because of deficits in related outcomes, such as cognition, and the added burdens of living with a chronic health condition. However, the associations between these outcomes and CHD have not been conclusively determined. Previous research has been limited by small convenience samples, a focus on more severe forms of CHD, lack of assessment in adolescents, and inadequate consideration of potential confounders. Additionally, some studies have focused on prediction while others have attempted to utilize a causal modeling strategy.

Dissertation Aims

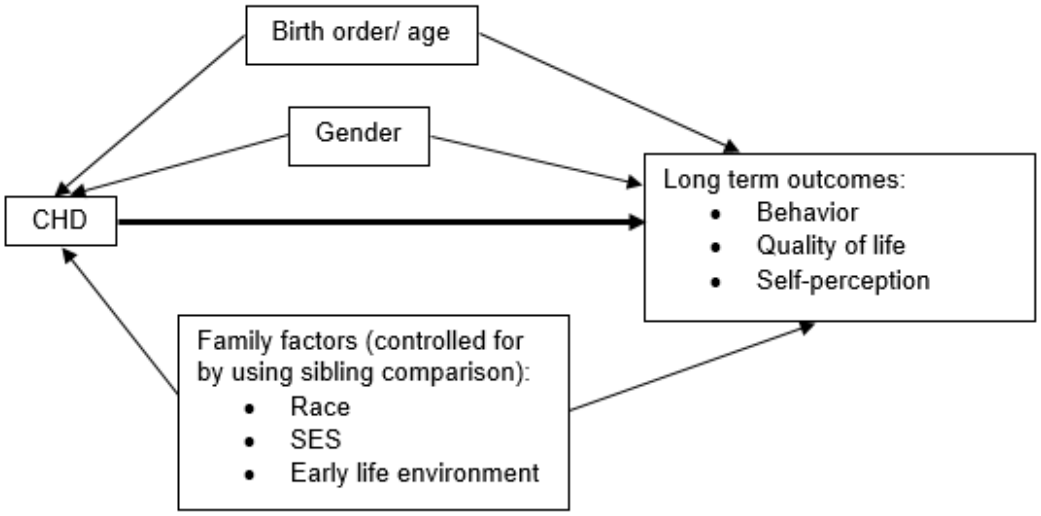
The goal of this dissertation is to address some of the limitations above to better understand behavior, quality of life, and self-perception in adolescents with CHD. This study proposes to evaluate these outcomes in a large sample of adolescents with surgically repaired CHD using parent- and patient-report. Scores for children with CHD will be compared to population norms, to an unaffected sibling, and between subgroups within the patient cohort. The use of siblings will help adjust for potentially biasing factors related to parental stress and other features of the family (Figure 1.1). The specific aims of this dissertation are:

Aim 1: Assess behavior problems in adolescents with CHD by comparing this group with an unaffected sibling and a normative population

Aim 2: Evaluate parent-reported quality of life in adolescents with CHD by comparing this group with an unaffected sibling and a normative population

Aim 3: Measure self-perception and self-reported quality of life in adolescents with CHD and compare these outcomes with normative samples.

Figure 1.1. Hypothesized relationships between long term outcomes and CHD addressed in this dissertation.



CHAPTER 2. BEHAVIOR IN ADOLESCENTS WITH CONGENITAL HEART DISEASE AND THEIR UNAFFECTED SIBLINGS

Background

Congenital heart disease (CHD) is the most common type of birth defect, affecting almost 1% of births in the United States.[1,2] Over the past several decades, there have been vast improvements in the likelihood that children with CHD survive into adulthood.[4,98] However, individuals with CHD have increased risk of genetic, neurological, and other medical comorbidities that may impact long term outcomes.[28,29,34,38,43,65,99] Thus, there is a need to understand cognitive and behavioral outcomes to maximize quality of life for these children.

Research thus far suggests that school-aged children with CHD have more behavior problems than healthy children.[57,59] These problems may become more prominent in adolescence when academic requirements and social interactions become more challenging.[53,100] This is a critical period of development because behavior problems can impact the development of risk-taking behaviors, negatively impacting adult health, and may hinder academic success, which may already be affected by neurocognitive deficits.[28,101,102] However, fewer previous studies have focused on this older age group and, those that have, generally had small sample sizes, focused on more severe forms of CHD,[43] recruited patients from a cardiac clinic setting which may not be representative of the full spectrum of patients with CHD,[103,104] and have inadequately considered unmeasured confounding by family characteristics.[57,58] The latter limitation primarily arises from using comparison groups for which information on important confounders is not available. Unaffected siblings provide a useful alternate comparison group for

addressing this issue because this comparison adjusts for shared familial factors including measurable confounders, such as socioeconomic status, but also factors that are difficult to measure, such as early life environment and parent perception of typical behavior. Therefore, the purpose of this study is to examine the relationship between CHD and behavior in adolescents using unaffected siblings for comparison.

Patients and Methods

Participants included all children born between 1998 and 2003 surgically treated for CHD at Children's Healthcare of Atlanta (CHOA). Cardiology surgical records, mortality information, and contact information were obtained from medical records. Contact information was also obtained by linking each child's parent to current addresses and telephone numbers using LexisNexis Accurint because children may not have been seen recently in CHOA facilities. We attempted to contact all families of the eligible children by mail and then by telephone if the family had not responded within two weeks. Children were excluded if they were known to be deceased, had inadequate contact information, or whose parents could not complete the questionnaires in English. We also excluded those with certain syndromes related to the outcomes of interest including 22q 11.2 deletion, Down, Holt-Oram, Loeys-Dietz, Triple X, Trisomy 18, Turner's, VACTERL, and William's.

Parents were asked to complete a questionnaire about their child with CHD and, if appropriate, about a sibling without a birth defect. To be eligible, the sibling had to be a full sibling, born between 1997 and 2004 who had not lived in a separate home from the child with CHD for more than a year. If more than one sibling met these criteria, the

parent was asked to complete the questionnaire about the sibling closest in age to the child with CHD.

Behavior

The outcome of interest was parent-reported behavior problems on the Child Behavior Checklist (CBCL). This is a well validated parent rating scale for children 6-18 years old. Of interest are three summary indices: internalizing, externalizing, and total behavior. Internalizing behavior includes anxious/depressed, withdrawn/depressed, and somatic complaints. Externalizing behavior includes aggressive and rule-breaking behaviors. Total behavior includes internalizing behavior, externalizing behavior, social problems, thought problems, and attention problems. Raw scores were converted to T scores which are standardized by age and gender (normative mean = 50, standard deviation = 10). Higher scores indicate more problems and scores in the top 10% of the normative sample (T score > 63) are considered to be clinically significant.[105]

Covariates

Diagnoses and treatment information from medical records were used to categorize CHD into three levels of severity. The most severe (e.g., hypoplastic left heart syndrome and other single ventricle diagnoses that require the Fontan circulation) were classified as critical single ventricle CHD. Children were classified with critical two ventricle CHD if they had a defect characterized by two functional ventricles but which requires surgery in the first year of life including coarctation of the aorta, critical aortic valve stenosis, critical pulmonary valve stenosis, d-transposition of the great arteries, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch,

pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, and truncus arteriosus. The remaining forms of CHD were classified as noncritical and considered the least severe (e.g., ventricular and atrial septal defects).[4]

We also considered the birth order of the child with CHD compared with the sibling because previous research has suggested that having a sibling with a chronic condition may affect the healthy child differently depending on which sibling is older.[106,107] Additionally, we considered *a priori* that the child with CHD may be more likely to be the younger sibling because of the relationship between maternal age and birth defects and the consideration that parents may stop having children after having a child with a CHD due to emotional or financial strain. Each pair was categorized as the child with CHD is the older of the pair, the sibling is older, or they are twins.

Comparison with normative data

Behavior problems were compared between our study sample of children with CHD and the expected value of 50 using one sample t tests and sign tests for the mean and median scores in each of the three scales. The binomial distribution was used to compare the proportion who scored in the clinical range to the expected value of 10%. Continuous scores and the proportion in the clinical range were also compared within the CHD group by defect severity.

To address potential selection bias due low response we conducted a sensitivity analysis using inverse probability of treatment weighting. Characteristics related to response from medical records and contact information were used to create the weights.

These were then applied to calculate adjusted estimates of the prevalence of behavior problems in the adolescents with CHD.

Comparison with siblings

To compare the continuous behavior scores between siblings the difference in scores for each pair was calculated by subtracting the score of the unaffected sibling from the child with CHD's score. Therefore, a positive difference indicates more behavior problems in the child with CHD than their sibling. The mean and median of these differences was compared with the null hypothesis of zero using t tests and sign tests. The proportion scoring in the clinical range was compared between siblings using the McNemar test. Additionally, conditional logistic regression was conducted for each behavior category. Interaction by CHD severity and birth order was assessed in these models.

All analyses were conducted using SAS 9.4 (Carey, NC). This study was approved by the IRB of Emory University and Children's Healthcare of Atlanta.

Results

Of the 1532 eligible adolescents with CHD we attempted to contact, 500 families (32.6%) participated. Two of these were excluded because an older sibling completed the parent questionnaire, one parent completed the questionnaire about the wrong child, and 14 parents did not answer enough items on the CBCL to calculate accurate scores. Therefore, 483 adolescents with CHD were included in this analysis. Of the participants with CHD, more than half were male, their median age was 14 (range: 11-18) at the time of the survey, and the majority were non-Hispanic white. Almost half, 47%, had

noncritical CHD, 35% were classified as critical two ventricle, and 17% as critical single ventricle. Biological mothers completed the majority of the parent questionnaires (Table 2.1).

Table 2.1. Characteristics of participating families with an adolescent surgically treated for congenital heart disease

Demographic characteristics of child with CHD		Participants N = 483
Gender	**Male**	264 (54.7%)
	Female	219 (45.3%)
Age at survey	**11**	14 (2.9%)
	12	97 (20.1%)
	13	93 (19.3%)
	14	88 (18.2%)
	15	75 (15.5%)
	16	68 (14.1%)
	17	46 (9.5%)
	18	2 (0.4%)
Race/ethnicity	**Non-Hispanic white**	308 (64.6%)
	Non-Hispanic black	108 (22.6%)
	Hispanic	33 (6.9%)
	Other	28 (5.9%)
Clinical characteristics of child with CHD		
Type of CHD	**Critical single ventricle**	83 (17.2%)
	Critical 2 ventricle	171 (35.4%)
	Noncritical	229 (47.4%)
Number of surgeries	**1**	324 (67.1%)
	2	77 (15.9%)
	3	42 (8.7%)
	4+	40 (8.3%)
Age at 1st surgery	**< 1 month**	121 (25.1%)
	1 - 6 months	118 (24.5%)
	6 months - 2 years	126 (26.1%)
	> 2 years	117 (24.3%)
Characteristics of the responder		

Relation to child with CHD	**Biological mother**	403 (84.5%)
	Biological father	56 (11.7%)
	Grandmother	7 (1.5%)
	Other	11 (2.3%)
Highest level of education	**< High school diploma/GED**	42 (8.8%)
	High school diploma/GED - some college	198 (41.7%)
	4 year college degree	141 (29.7%)
	> 4 year college degree	94 (19.8%)
Annual household income	**< $25,000**	88 (18.9%)
	$25,000 - $50,000	84 (18.1%)
	$50,000 - $100,000	138 (29.7%)
	>$100,000	155 (33.3%)
Marital status	**Married**	348 (72.8%)
	Living with partner	6 (1.3%)
	Divorced, separated, widowed	88 (18.4%)
	Never married	36 (7.5%)

Of the 483 families with complete behavior information, 212 (43.9%) parents also completed the CBCL for an eligible sibling. These siblings consisted of slightly more females (55.9%) than males with a median age of 14 (range: 10-18) (Table 2.2). In 48% of these pairs, the sibling was older than the child with CHD, in 44% the child with CHD was older, and in 8% the child with CHD and sibling were twins.

Table 2.2. Distribution of gender and age for adolescents with CHD and their unaffected siblings included in the sibling analysis

Demographic characteristics		CHD with sibling N = 212	Siblings N = 212
Gender	**Male**	114 (53.8%)	93 (44.1%)
	Female	98 (46.2%)	118 (55.9%)
Age at survey	**10**	0 (0.0%)	6 (2.8%)
	11	3 (1.4%)	33 (15.6%)
	12	36 (17.0%)	27 (12.7%)
	13	48 (22.6%)	23 (10.9%)
	14	46 (21.7%)	28 (13.2%)
	15	33 (15.6%)	29 (13.7%)
	16	26 (12.3%)	30 (14.2%)
	17	19 (9.0%)	20 (9.4%)
	18	1 (0.5%)	16 (7.6%)

Comparison with Normative Data

On average, the adolescents with CHD were reported to have similar levels of behavior problems as the normative sample on total behavior (median = 50), but had more reported behavior problems on average in internalizing behavior (median = 53) and lower than expected on externalizing behavior (median = 46). When grouped by CHD type there was also a statistically significant positive trend between total and internalizing behavior and severity (Table 2.3). A greater than expected proportion of children with CHD were reported to have behavior problems in the clinical range except for in externalizing behavior (total behavior: 18.2%, 95% CI = 14.9-22.0; internalizing behavior: 20.5%, 95% CI = 17.0-24.4; externalizing behavior: 8.5%, 95% CI = 6.2-11.3). As CHD severity increased, there was also an increasing trend in the proportion of children with behavior problems in the clinical range. For example, over one-third of adolescents with a critical single ventricle defect scored in the clinical range in

internalizing behavior (prevalence = 34.9%, 95% CI: 24.8 – 46.2). Nevertheless, even for those with noncritical CHD this proportion was higher than expected in total (prevalence = 14.0, 95% CI: 9.8 – 19.2) and internalizing behavior (prevalence = 14.4%, 95% CI: 10.1 – 19.6) (Figure 2.1).

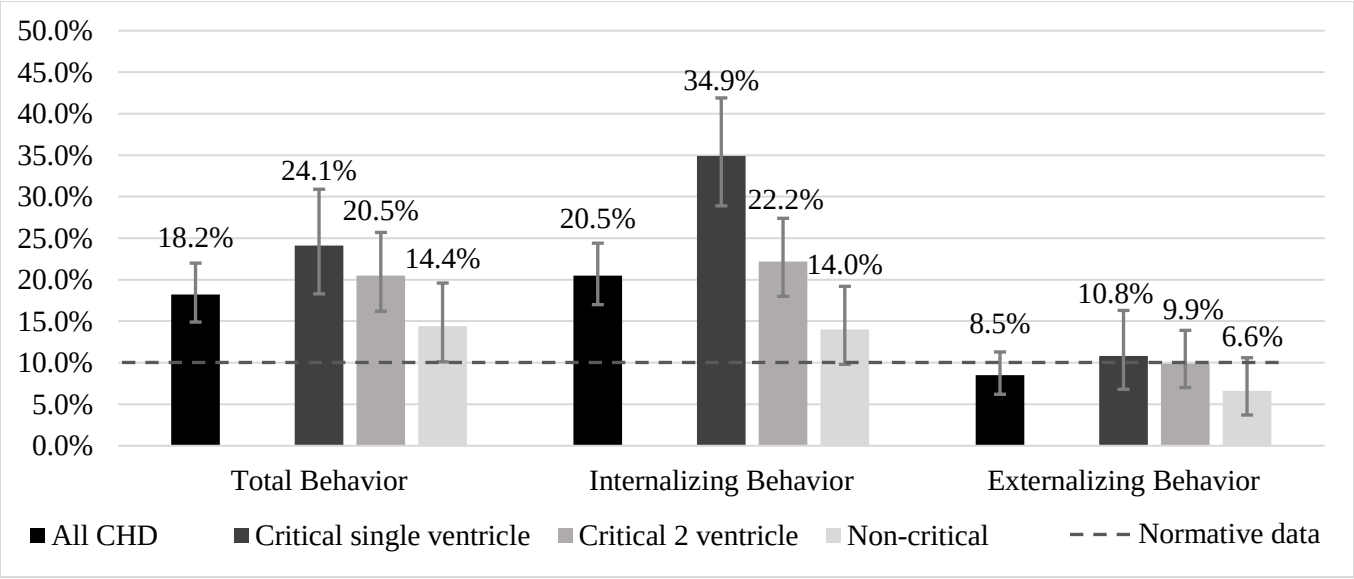
Table 2.3. Distribution of behavior scores for normative data, children with CHD, and siblings

		Normative data[1]	Children with CHD N = 483	p-value[2]	Critical 1 ventricle N = 83	Critical 2 ventricle N = 171	Noncritical N = 229
Total Behavior	**Mean (std dev)**	50.0 (10.0)	50.6 (12.0)	0.26	54.3 (11.2)	50.9 (12.4)	49.0 (11.8)
	Median (range)	50.0	50.0 (24, 84)	0.61	55.0 (27, 75)	51.0 (27, 76)	48.0 (24, 84)
Internalizing Behavior	**Mean (std dev)**	50.0 (10.0)	53.2 (11.5)	<0.01	57.2 (11.5)	53.1 (12.1)	51.8 (10.8)
	Median (range)	50.0	53.0 (33, 91)	<0.01	57.0 (33, 78)	52.0 (33, 81)	52.0 (33, 91)
Externalizing Behavior	**Mean (std dev)**	50.0 (10.0)	47.4 (10.4)	<0.01	49.1 (10.6)	47.4 (10.6)	46.9 (10.2)
	Median (range)	50.0	46.0 (34, 82)	<0.01	49.0 (34, 80)	46.0 (34, 80)	46.0 (34, 82)

[1]These expected values are standardized T scores derived using a healthy sample of children from the general population

[2]Comparison of all children with CHD with expected value from normative data, means compared using t test and medians using sign test

Figure 2.1. Prevalence and 95% confidence intervals of adolescents with reported behavior scores in the clinically significant range for all participants with CHD and by CHD severity



Bivariate analyses revealed that responders were seen more recently at CHOA, had undergone more surgeries, and were more likely to have linked to contact information from Accurint than nonresponders (Table 2.4). After adjusting for these factors using inverse probability of treatment weighting so that the responders better represented the baseline cohort, the new estimates of the prevalence of behavior problems in the clinical range were slightly attenuated, but not meaningfully different, than the unweighted estimates (Table 2.5).

Table 2.4. Demographic, clinical, and recruitment characteristics of responders and nonresponders

		Responders N = 483 (32%)	Nonresponders N = 1048 (68%)	p-value
Gender	**Male**	33%	67%	0.32
	Female	30%	70%	
Year of birth	**1998**	35%	65%	0.58
	1999	27%	73%	
	2000	31%	69%	
	2001	33%	67%	
	2002	33%	67%	
	2003	31%	69%	
Type of CHD	**Critical single ventricle**	37%	63%	0.20
	Critical 2 ventricle	31%	69%	
	Noncritical	30%	70%	
Last CHOA DOS	**< 4.25 yrs ago**	40%	60%	<0.01
	4.25-6.75 yrs ago	32%	68%	
	6.75-12 yrs ago	29%	71%	
	>12 yrs ago	27%	73%	
Number of surgeries	**1**	30%	70%	0.04
	2	33%	67%	
	3	35%	65%	
	4+	43%	57%	

Age at 1st surgery	**< 1 month**	33%	67%	0.91
	1 - 6 months	30%	70%	
	6 months - 2 years	32%	68%	
	> 2 years	31%	69%	
Accurint address available	**Yes**	35%	65%	<0.01
	No	14%	86%	
Wave of recruitment	**1**	34%	66%	0.10
	2	40%	60%	
	3	31%	69%	
	4	29%	71%	
	5	31%	69%	
	6	25%	75%	
	7	31%	69%	

Table 2.5 Assessment of potential selection bias in the prevalence of behavior problems in the clinical range for all adolescents with CHD by comparing the crude/unadjusted estimates and the estimates adjusted by applying inverse probability of treatment weighting.

	Prevalence in clinically significant range	
Behavior scale	**Unadjusted**	**Adjusted using IPTW[1]**
Total	18.2%	17.7%
Internalizing	20.5%	20.0%
Externalizing	8.5%	8.0%

[1]Inverse probability of treatment weighting attempted to balance characteristics between responders and nonresponders. The weight was created from a propensity score including in the model the wave of recruitment, whether the parent linked to Accurint, last date of service at Children's Healthcare of Atlanta, total number of surgeries, and CHD severity.

Comparison with Sibling

On average adolescents with CHD were reported to have more behavior problems and internalizing behavior problems (median difference = 5.0 and 4.3 respectively), but not externalizing behaviors, than their unaffected siblings (Table 2.6). Those with CHD

also had a higher prevalence of clinically significant behavior than their siblings (total: 14.2% vs 8.0%, internalizing: 17.0% vs. 9.4%, externalizing: 5.6% vs. 2.4%) (Figure 2.2). This translated to more than a two times greater odds of the adolescent with CHD being in the clinical range compared with their sibling on all behavior scales. There was no statistically significant interaction by severity of CHD, but the estimates for total and internalizing behavior were modified by whether the child with CHD was older or younger. Specifically, there was no association between having CHD and reported behavior problems if the child with CHD was older than the sibling. However, in pairs where the adolescent with CHD was younger, the odds of having behavior problems in the clinically significant range was 6.5 and 8.5 times greater than the sibling for total and internalizing behavior respectively (Table 2.7). There were too few sets of twins to look at these pairs separately.

Table 2.6. Distribution of behavior scores for children with CHD included in the sibling analysis and their unaffected siblings

		CHD with sibling N = 212	Sibling N = 212	Difference	p-value[1]
Total Behavior	**Mean (std dev)**	49.2 (11.3)	44.1 (11.8)	5.0 (11.8)	<0.01
	Median (range)	48.0 (24, 73)	45.0 (24, 73)	5.0 (-38, 33)	<0.01
Internalizing Behavior	**Mean (std dev)**	51.8 (11.2)	47.4 (10.8)	4.3 (11.9)	<0.01
	Median (range)	51.0 (33, 81)	47.0 (33, 78)	4.0 (-33, 33)	<0.01
Externalizing Behavior	**Mean (std dev)**	45.7 (10.1)	44.3 (9.6)	1.3 (11.0)	0.10
	Median (range)	44.0 (34, 82)	43.0 (34, 75)	0.0 (-35, 42)	0.09

[1]Comparison between sibling pairs evaluated by comparing difference with 0, means compared using t test, medians using sign test

Figure 2.2. Prevalence and 95% confidence intervals of adolescents with reported behavior scores in the clinically significant range compared between those with CHD and their unaffected siblings

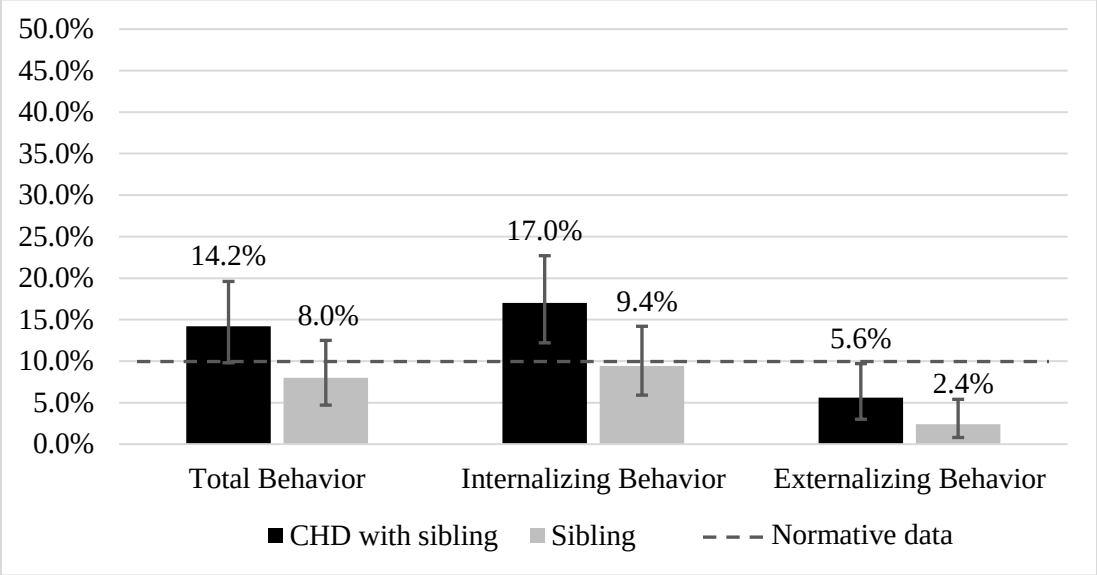


Table 2.7. Odds ratios and 95% confidence intervals of scoring in the clinically significant range comparing children with CHD to a similarly aged unaffected sibling

Behavior Scale		N pairs	OR	95% CI
Total	**Unadjusted**	212	2.6	1.2 - 5.9
	Sibling older[1]		6.5	1.5 - 28.8
	CHD older		0.8	0.3 - 2.7
Internalizing	**Unadjusted**	212	2.2	1.2 - 4.3
	Sibling older[1]		8.5	2.0 - 36.8
	CHD older		1.0	0.4 - 2.4
Externalizing	**Unadjusted**[2]	212	2.8	0.9 - 8.6

[1]There were too few twin pairs to estimate reliable odds ratios so they are not shown separately here

[2]There was no interaction by birth order in the effect of CHD on externalizing behavior

Discussion

This study suggests that adolescents with CHD have more behavior problems, particularly internalizing behavior problems, than healthy peers, even those with noncritical CHD. Generally, the sibling comparison agreed with these results, finding that adolescents had more behavior problems than their unaffected siblings.

Prior results have been mixed on the association between CHD and behavior. One study of children 7-17 years old who were surgically treated for one type of CHD had comparable total behavior problems to what we observed.[57] Other evidence also supports this trend of more behavior problems in those with CHD,[51,100] however, some studies have suggested no difference or that adolescents with CHD have fewer behavior problems than healthy controls.[58,103] Additionally, a number of other studies have not observed increasing behavior problems with greater CHD severity as we saw in our

unadjusted analyses,[51,104,108] although we did not find significant differences by severity when we looked at the odds ratio for scoring in the clinically significant range. This may suggest that the unadjusted effect of severity we observe is due to confounding that is adjusted for in the sibling analyses, or that both our conditional logistic regression analysis and previous studies have not had adequate power to observe differences at that level of stratification. Evidence from several studies suggest the latter may be possible because a meaningful difference can be observed in the estimates for different types of CHD even though the difference did not reach statistical significance.[104,108] To our knowledge, only one other published study has compared behavior problems between adolescents with CHD and an unaffected sibling. Although this study included only 31 children with CHD and 18 healthy siblings, the authors found a significant difference between mean t scores and the proportion in the clinical range in behavior problems consistent with our findings.[109]

Our results suggest that the impact of CHD on behavior may be modified by birth order and/or family structure. It is unclear why an adolescent with CHD would only have more clinically significant behavior problems than their sibling in pairs where the child with CHD is younger. In fact, this finding is contradictory to other studies in which older siblings of children with chronic conditions reported more of a burden potentially due to increased responsibility, including caregiver tasks, and less time with parents.[110-112] Research suggests having a child with a chronic condition in the family affects the behavior of all siblings through parental stress,[113] and perhaps in families where the child with CHD is older or a twin, the sibling would experience this familial strain the most because it would be present throughout their entire life. In our study, although the

unaffected siblings had fewer reported behavior problems than the normative sample, among this group we found more reported behavior problems in those with an older brother or sister with CHD compared with those with a younger sibling who has CHD (results not shown).

It is also noteworthy that the adolescents with CHD who had a sibling in the study had less behavior problems in all three scales compared with the rest of the CHD group. It could be that if the first child has more severe health problems the parents choose not to have another child, whereas if the defect is more minor the parents have more children. Our data does not support this as 53% of children with critical single ventricle had a younger sibling compared with 41% and 43% in children with critical two ventricle and noncritical CHD respectively, but there may be a different pattern within these broad categories. It is also possible that having a similarly aged sibling serves as a buffer for the child with CHD and gives them a reference for normal behavior. Similarly, the presence of healthy children in the family could affect the parent's perspective of what typical behavior is.

Strengths of this study include the use of unaffected siblings as a comparison group which controls potential confounding by shared familial factors such as socioeconomic status, early life environment, and parental perception of behavior. Also, compared to previous studies our baseline cohort of eligible children with CHD is more representative of the general population of children surgically treated for CHD. This is because CHOA treats almost all cases of CHD in Georgia, and participants did not need to be current patients who would likely have more severe forms of CHD and higher socioeconomic status.[114] By recruiting outside the clinic setting and including all types of

CHD we were also able to look at behavior problems in children with less severe defects. To classify CHD severity, we had the advantage of using diagnoses and surgical information. This is ideal over using ICD-9 codes because some defects can be placed in two different categories depending on the severity of symptoms within the individual.

Despite the advantages of our study we did have several limitations including the low response rate. Our sensitivity analysis suggests no important selection bias from nonresponse, but we cannot eliminate the possibility that we did not see a change with the adjusted estimates because we were unable to account for an important covariate such as socioeconomic status. Additionally, our sample size was too small for certain subanalyses such as assessing behavior by specific types of defects. Related to this, only half of the original sample of children with CHD had an eligible sibling. Therefore, the results of the sibling comparison may not be generalizable to the entire CHD population, particularly since the children with CHD who had a sibling in the study had fewer behavior problems than other adolescents with CHD. In fact, the estimates of the effect of CHD on behavior may be conservative in the sibling comparison if the presence of a child with a chronic condition in the family affects the entire family as mentioned above. Finally, behavior was only measured by parent report which can be influenced by their own mental health problems and adjustment to having a child with CHD.[67,115] This could somewhat be accounted for in the sibling comparison, but parents may still have different expectations of behavior between their child with CHD and a sibling without health problems.

Conclusion

This study used comparison with unaffected siblings to strengthen the evidence that adolescents with CHD have an increased prevalence of total and internalizing behavior problems compared with healthy children and teens. Although this has previously been accepted for children with more severe forms of CHD, our results suggest that all children surgically treated may have an increased risk for behavior problems. This highlights the need for clinicians and parents to monitor these children so that intervention services can be initiated as early as possible. The findings of the study also raise the issue of the role of a healthy sibling in the development of a child with CHD. Further research should be done to explore this relationship and investigate why birth order may modify the effect of having a CHD on behavior.

CHAPTER 3. PARENT-REPORTED QUALITY OF LIFE IN ADOLESCENTS WITH CONGENITAL HEART DISEASE: A SIBLING STUDY

Introduction

Congenital heart disease (CHD) affects almost 1% of births in the United States making it the most common type of birth defect.[1,2] Advancements in treatment over the last several decades have dramatically improved the survival rate in these patients so that, recently, 85-90% were estimated to reach adulthood.[4,98] Additionally, one study estimated that the median age of patients with CHD increased from 11 years in 1985 to 17 years in 2000 and that this age is likely to continue increasing.[116] This shift in the age of survivors necessitates research on the long term impacts of this condition and its treatments. Previous studies suggest that children with CHD are more likely to experience cognitive deficits compared with healthy peers including increased prevalence of developmental disabilities, lower social cognition, speech and language difficulties, and poorer executive functioning[28,100] Children with CHD, especially those with more severe forms, may also have real or perceived exercise restrictions that lead to limited involvement in sports, inadequate physical activity, and obesity.[94,117-119] All of these issues could contribute to poorer quality of life (QOL) which is an important outcome to assess because the well-being of these individuals should be optimized in addition to survival. Quality of life considers more than the physical morbidity of a chronic condition by combining it with an individual's perception of psychological and social functioning.[120] It is also an important outcome because it could help guide intervention services to improve functionality in this group.

Adolescense is a crucial developmental stage when individuals seek an independent identity, are faced with increase social pressures, and are at risk for developing unhealthy

habits.[101,102] This period is even more important for those with CHD because they must prepare to take responsibility of their own health and care of their condition.[121] Thus far, studies of quality of life that have included adolescents have found mixed results[81,82,122-125] One observation that has been consistent is the association between lower socioeconomic status (SES) and lower reported quality of life in both adolescents with CHD and the general population.[85,125-127] It is generally hypothesized that this association with SES may be due to differences in access to resources, parental attitudes towards and expectations of their children, and increased exposure to stressors for the parent and child.[126] Similarly, familial characteristics, including sense of coherence, parenting style, and parental stress and depression, have been related to reported quality of life in children with CHD.[88,125,128] Therefore, differences in SES and other family characteristics between patients with CHD and healthy populations may be confounding the effect of the CHD on quality of life. However, very few studies attempt to control for such factors which may be leading to some of the inconsistent findings. To address this limitation, this studies aims to assess the impact of CHD on quality of life by comparing affected adolescents with a sibling without a birth defect to control for shared family factors.

Methods

Data were obtained on all children born between 1998 and 2003 surgically treated for CHD 1998-2009 at Children's Healthcare of Atlanta (CHOA). Information on surgeries related to CHD treatment, mortality information, and contact information were obtained from CHOA clinical records. We obtained more updated contact information by linking the parent or guardian of each child to current addresses and telephone numbers using Accurint, a commercial company that provides contact information from

sources like credit cards, because children may not have been seen recently in CHOA facilities.

Children were excluded if they were known to be deceased (N = 235), had inadequate contact information (N = 117), or their parents could not complete the questionnaires in English (N = 9). We also excluded those with certain syndromes related to the outcomes of interest (N = 289) including 22q 11.2 deletion, Down, Holt-Oram, Loeys-Dietz, Triple X, Trisomy 18, Turner, VACTERL, and William's because the impact of these syndromes on quality of life would likely be greater than any potential impact from the CHD and its treatments.

We attempted to contact all families of the eligible children by mail and then by telephone if the family had not responded within two weeks. Parents were asked to complete a questionnaire about their child with CHD and another about a sibling without a birth defect if there was one. To be eligible, the sibling had to be a full sibling born between 1997 and 2004 who had not lived in a separate home from the child with CHD for more than a year. If more than one sibling met these criteria, the parent was asked to complete the questionnaire about the sibling closest in age to the child with CHD.

Quality of Life

The parent questionnaires included the Pediatric Quality of Life Inventory (PedsQL), Version 4.0, a well-validated instrument designed to measure health-related quality of life at various ages.[129,130] The generic core for children (8 – 12 years old) and teens (13 – 18 years old) includes physical functioning, emotional functioning, social functioning, and school functioning. Each item is ranked by the respondent on a Likert

scale from ‘never a problem’ to ‘always a problem’ for their child. Responses are then transformed to a scale of 0 to 100, and these scores are averaged across items for each scale. Higher scores indicate better quality of life. The physical health score is equivalent to the physical functioning score, and psychosocial health is the average of items in the emotional, social, and school functioning scales. All four separate scales are averaged for the total score. Cutpoints for clinically relevant reduced quality of life have been identified from application of the PedsQL in a large normative population of healthy children and teens and those with various chronic conditions. These cutpoints represent one standard deviation below the population mean in the normative sample.[129]

Covariates

Diagnoses and treatment information from clinical records were used to categorize each child’s CHD into three levels of severity. Critical single ventricle CHD represents the most severe forms including hypoplastic left heart syndrome and other single ventricle diagnoses that require the Fontan circulation or transplant. Children were classified as having critical two ventricle CHD if they had other forms of critical CHD that require treatment in the first year of life. These include coarctation of the aorta, critical aortic valve stenosis, critical pulmonary valve stenosis, d-transposition of the great arteries, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, and truncus arteriosus. The remaining forms of CHD were classified as noncritical and considered least severe. These included ventricular and atrial septal defects among others.[4]

We also considered the birth order of the child with CHD compared with the sibling because previous research has suggested that having a sibling with a chronic condition may affect the unaffected child differently depending on which sibling is older.[106] Additionally, we considered a priori that the child with CHD may be more likely to be the younger sibling because of the relationship between maternal age and birth defects and the consideration that parents may stop having children after having a child with a CHD due to emotional and/or financial strain.[115] The sibling pairs were grouped based on whether the child with CHD is the older sibling, the younger sibling, or a twin.

Analysis

Demographic and clinical characteristics were described of the patients with CHD, the parent or guardian respondent, and the unaffected sibling. Age and gender were compared between the CHD and sibling groups using a paired t test and McNemar test respectively. Parent-reported scores for each scale were compared between the child with CHD and their sibling using paired t-tests for the means and sign ranked tests for the medians. Linear regression was used to assess the effect of CHD on quality of life. Each model included dummy variables to account for the sibling pair as a fixed effect. Therefore, the estimate of the effect of CHD can be interpreted as the mean difference in scores between the child with CHD and their sibling. A negative effect indicates that the child with CHD had a lower (worse) score on that quality of life scale. The PedsQL cutoff points were used to dichotomize scores in each scale by whether the score was low enough to be clinically relevant. The proportion falling below these thresholds were compared between the sibling groups using the McNemar test. Conditional logistic

regression was also used to compare the odds of scoring below this level between pairs. Gender and age for each child were included in the adjusted models as potential confounders. We also assessed potential effect modification by CHD severity and birth order. Although we were not concerned about potential selection bias due low response in our sibling comparison, this bias could impact our estimates of quality of life in our sample of adolescents with CHD and the comparison of this group with the normative population. Therefore, to address this potential issue we conducted a sensitivity analysis using inverse probability of treatment weighting. Characteristics related to response from medical records and contact information were used to create the weights. These were then applied to calculate adjusted estimates of the prevalence of quality of life below the clinical relevant cutpoints in the adolescents with CHD.

Results

Of the 1532 eligible adolescents with CHD we attempted to contact, 497 (32%) parents returned a completed questionnaire about their child with CHD. Eleven parents did not answer enough items in the PedsQL to calculate accurate scores resulting in 486 families to be included in this analysis. Among participating families, 217 (45%) parents also completed this section for an eligible sibling. In those who did not return a sibling questionnaire, 18 parents reported an eligible sibling in the family but chose not to complete the relevant questionnaire and the rest reported no eligible sibling.

Demographic and clinical characteristics of the adolescents and their parents are shown in Table 3.1. In all participanting families, the adolescents with CHD were 55% male, with a median age of 14 (range = 11 – 18) at the time of the survey, and the majority were non-Hispanic white. Almost half, 47%, had noncritical CHD, 36% were

classified as critical two ventricle, and 17% as critical single ventricle. Biological mothers completed the majority of the parent questionnaires. Among families who completed the sibling questionnaire, the unaffected siblings consisted of slightly more females (56%) than the group with CHD but were similar in age (median age = 14, range = 10 – 18). In 47% of these pairs, the sibling was older than the child with CHD, in 45% the child with CHD was older, and in 8% the child with CHD and sibling were twins.

Table 3.1. Characteristics of CHD patients and their parent responders

Demographic characteristics		All CHD patients N = 486	CHD with siblings N = 217
Age at survey	**Mean (SD)**	14.5 (1.7)	14.5 (1.6)
	Median (Range)	14 (11 - 18)	14 (11 - 18)
Gender	**Male**	266 (54.7%)	116 (53.5%)
Race/ethnicity	**Non-Hispanic white**	313 (64.9%)	158 (73.5%)
	Non-Hispanic black	106 (22.0%)	32 (14.9%)
	Hispanic	34 (7.1%)	10 (4.7%)
	Other	29 (6.0%)	15 (7.0%)
Clinical characteristics			
Type of CHD	**Critical single ventricle**	82 (16.9%)	39 (18.0%)
	Critical 2 ventricle	176 (36.2%)	76 (35.0%)
	Noncritical	228 (46.9%)	102 (47.0%)
Number of surgeries	**1**	326 (67.1%)	152 (70.1%)
	2	78 (16.1%)	29 (13.4%)
	3	43 (8.9%)	20 (9.2%)
	4+	39 (8.0%)	16 (7.4%)
Age at 1st surgery	**< 1 month**	127 (26.2%)	59 (27.2%)
	1 - 6 months	117 (24.1%)	50 (23.0%)
	6 months - 2 years	125 (25.8%)	49 (22.6%)
	> 2 years	116 (23.9%)	59 (27.2%)
Characteristics of the responder			
Relation to child with CHD	**Biological mother**	407 (84.4%)	185 (85.3%)
	Biological father	57 (11.8%)	26 (12.0%)
	Grandmother	7 (1.5%)	3 (1.4%)
	Other	11 (2.3%)	3 (1.4%)
Highest level of education	**< High school diploma/GED**	42 (8.8%)	15 (6.9%)
	High school diploma/GED - some college	201 (41.9%)	69 (35.2%)
	4 year college degree	143 (29.8%)	76 (35.2%)
	> 4 year college degree	94 (19.6%)	56 (25.9%)
Annual household income	**< $25,000**	87 (18.5%)	20 (9.5%)
	$25,000 - $50,000	88 (18.7%)	35 (16.6%)
	$50,000 - $100,000	140 (29.8%)	59 (28.0%)
	>$100,000	155 (33.0%)	97 (46.0%)

Marital status	**Married**	350 (72.5%)	174 (80.2%)
	Living with partner	7 (1.4%)	2 (1.0%)
	Divorced, separated, widowed	90 (18.6%)	33 (15.2%)
	Never married	36 (7.5%)	8 (3.7%)

Parent-reported quality of life for all participants with CHD was lower on all scales compared with the normative sample. When the sample with CHD was limited to those who had an unaffected sibling in the study there was no difference with normative means on the composite scales, and emotional and social functioning were higher in the CHD group than the normative sample. Nevertheless, parents reported lower quality of life for the adolescent with CHD compared with their unaffected sibling on all scales (Table 3.2).

Table 3.2. Parent-report of quality of life from PedsQL 4.0 Generic Core for participants with CHD and their unaffected siblings

		Normative sample	All CHD N = 486	CHD with sibling N = 217	Sibling N = 217
Total[a, b, c]	**Mean (SD)**	*81.3 (15.9)*	78.4 (17.9)	82.6 (15.5)	89.8 (11.6)
	Median (IQR)		82.6 (66.3, 93.5)	87.5 (72.8, 95.7)	94.6 (84.8, 98.9)
Physical health[a, c, d]	**Mean (SD)**	*83.3 (20.0)*	80.1 (21.8)	83.9 (19.0)	91.5 (14.1)
	Median (IQR)		87.5 (68.8, 100)	90.6 (75, 100)	100.0 (90.6, 100)
Psychosocial health[a, c, d]	**Mean (SD)**	*80.2 (15.8)*	77.5 (18.3)	81.9 (16.2)	88.9 (12.6)
	Median (IQR)		81.0 (65.0, 93.3)	85.0 (73.3, 96.7)	93.3 (83.3, 100)
Emotional functioning[b, c, d]	**Mean (SD)**	*80.3 (17.0)*	81.6 (20.1)	84.3 (18.3)	88.0 (15.4)
	Median (IQR)		90.0 (70.0, 100)	90.0 (70.0, 100)	95.0 (80.0, 100)
Social functioning[a, b, c, d]	**Mean (SD)**	*82.2 (20.1)*	79.4 (22.1)	84.7 (19.1)	92.5 (14.2)
	Median (IQR)		85.0 (60.0, 100)	95.0 (70.0, 100)	100 (95.0, 100)
School functioning[a, c, d]	**Mean (SD)**	*76.9 (20.2)*	71.7 (22.3)	76.7 (20.6)	86.3 (16.8)
	Median (IQR)		75.0 (55.0, 90.0)	80.0 (60.0, 95.0)	90.0 (80.0, 100)

[a] Parent-reported quality of life statistically different **between all participants with CHD and the normative sample** using one sample t tests (means)
[b] Parent-reported quality of life statistically different **between adolescents with CHD with an eligible sibling and the normative sample** using one sample t tests (means)
[c] Parent-reported quality of life statistically different **between unaffected siblings and the normative sample** using one sample t tests (means)
[d] Parent-reported quality of life statistically different **between adolescents with CHD and their unaffected sibling** using paired t tests (means) and sign rank tests (medians)

Using paired analyses, parent-report of physical health and psychosocial health were 7.6 and 7.0 points lower, respectively, for the adolescents with CHD than their sibling (95% CIs: physical = -11.4, -3.8; psychosocial = -10.0, -4.0). Among the measured scales, the average difference in scores between siblings was greatest in school functioning (mean difference = -9.6; 95% CI = -13.0, -5.3) and smallest in emotional functioning (mean difference = -3.7, 95% CI = -7.2, -0.2). Estimated differences did not meaningfully change after adjustment for age and gender (Table 3.3). When stratified by CHD severity, there was a larger difference between the CHD and sibling groups for those with critical single ventricle (total QoL mean difference = -15.7, 95% CI = -23.9, -7.5) than the other two severity groups. Differences between sibling pairs were similar for the critical double ventricle (total QoL mean difference = -4.6, 95% CI = -9.8, 0.7) and noncritical groups (total QoL mean difference = -5.5, 95% CI = -9.7, -1.3), and mostly still meaningfully different than zero in all areas except emotional functioning (Table 3.4). There was no interaction by birth order.

Table 3.3. Estimated effects of the presence of a CHD on quality of life comparing adolescents with CHD to their unaffected sibling

	Unadjusted		Adjusted[b]	
	Mean difference[a]	**95% CI**	**Mean difference[a]**	**95% CI**
Total	-7.2	-10.0, -4.4	-7.1	-10.1, -4.1
Physical health	-7.6	-11.4, -3.8	-7.6	-11.4, -3.7
Psychosocial health	-7.0	-10.0 -4.1	-6.8	-10.1, -3.5
Emotional functioning	-3.7	-7.2, -0.2	-3.9	-7.5, -0.2
Social functioning	-7.8	-11.6, -4.0	-7.5	-11.9, -3.2
School functioning	-9.6	-13.9, -5.3	-9.0	-13.5, - 4.6

[a]Mean differences were calculated using fixed effects linear models with dummy variables included to account for sibling pairs
[b]Adjusted for age and gender

Table 3.4. Estimated effects of the presence of a CHD on quality of life comparing adolescents with CHD to their unaffected sibling using fixed effects linear regression stratified by CHD severity

	Critical Single Ventricle (N = 39 pairs)		Critical Two Ventricle (N = 76 pairs)		Noncritical (N = 102 pairs)	
	Mean difference[a]	95% CI	Mean difference	95% CI	Mean difference	95% CI
Total	-15.7	-23.9, -7.5	-4.6	-9.8, 0.7	-5.5	-9.7, -1.3
Physical health	-16.2	-28.3, -4.1	-4.6	-11.6, 2.3	-5.9	-11.1, -0.7
Psychosocial health	-15.5	-23.8, -7.31	-4.6	-10.2, 1.1	-5.3	-10.0, -0.6
Emotional functioning	-10.7	-20.2, -1.2	-1.9	-9.6, 5.8	-3.1	-7.9, 1.7
Social functioning	-19.4	-30.8, -8.1	-4.1	-10.9, 2.8	-6.3	-13.1, 0.5
School functioning	-16.5	-26.7, 6.3	-7.7	-14.8, -0.6	-6.4	-13.0, 0.2

[a]All estimates are adjusted for age and gender

The percent of adolescents below the clinical cutpoint (< 1 standard deviation below mean in normative population) was higher for the full sample with CHD compared with the normative population in all scales except emotional functioning. Bivariate analyses revealed that responders were seen more recently at CHOA, had undergone more surgeries, and were more likely to have linked to contact information from Accurint than nonresponders. After adjusting for these factors using inverse probability of treatment weighting so that the responders better represented the baseline cohort, the new estimates of the prevalence of low quality of life were slightly higher, but not meaningfully different, than the unweighted estimates (weighted vs. unadjusted %: total = 25.1% vs. 24.3%; physical health = 22.9% vs. 21.8%; psychosocial health = 25.1% vs. 24.5%).

The prevalence of parent-reported low quality of life was also higher for the adolescents with CHD compared with the sibling group in all areas. Among the group with CHD with a sibling, 15.7% (95% CI: 10.8-20.5%) and 16.6% (95% CI: 11.6-21.5%) scored below this cutpoint in physical and psychosocial health respectively compared with 8.3% (95% CI: 4.6-12.0%) and 5.1% (95% CI: 2.2-8.0%) in the siblings (Table 3.5). After adjustment for age and gender, the teens with CHD had a two times greater odds of scoring below this cutpoint in the physical health (95% CI: 0.9, 4.4) than their sibling and a four times greater odds in psychosocial health (95% CI: 1.9, 10.0) (Table 3.6). We also attempted to assess effect modification by CHD severity, but do not present the results here because the results became unstable at that level of stratification.

Table 3.5. Comparison of the prevalence (95% CI) between adolescents with CHD and unaffected siblings with parent-reported quality of life in the clinically relevant range (< 1 standard deviation below mean in normative sample)

	Normative sample	**All CHD**	**CHD with sibling**	**Sibling**
		N = 486	**N = 217**	**N = 217**
Total [a, c, d]	*18%*	24.3% (20.5, 28.1)	16.6% (11.6, 21.5)	5.1% (2.2, 8.0)
Physical health [a, c, d]	*17%*	21.8% (18.1, 25.5)	15.7% (10.8, 20.5)	8.3% (4.6, 12.0)
Psychosocial health [a, c, d]	*18%*	24.5% (20.7, 28.3)	16.6% (11.6, 21.5)	5.1% (2.2, 8.0)
Emotional functioning [a, c, d]	*16%*	18.9% (15.5, 22.4)	14.3% (9.6, 18.9)	9.2% (5.4, 13.1)
Social functioning [a, c, d]	*19%*	25.5% (21.6, 29.4)	19.4% (14.1, 24.6)	5.1% (2.2, 8.0)
School functioning [a, c, d]	*19%*	27.6% (23.7, 31.6)	19.8% (14.5, 25.1)	8.7% (5.0, 12.5)

[a] Proportion significantly different **between all participants with CHD and the normative sample** using the binomial distribution

[b] Proportions not significantly different on any scale **between adolescents with CHD with an eligible sibling and the normative sample** using the binomial distribution

[c] Propotion significantly different **between unaffected siblings and the normative sample** using the binomial distribution

[d] Proportion significantly different **between adolescents with CHD and their unaffected sibling** using the McNemar test

Table 3.6. Comparison of parent-reported quality of life in the clinically relevant range (< 1 standard deviation below mean in normative sample) between adolescents with CHD and their unaffected siblings using conditional logistic regression

	Unadjusted		Adjusted[a]	
	OR	**95% CI**	**OR**	**95% CI**
Total	6.0	2.3, 15.5	10.3	2.2, 48.9
Physical health	2.3	1.2, 4.6	2.0	0.1, 4.4
Psychosocial health	4.1	1.9, 8.9	4.3	1.9, 10.0
Emotional functioning	2.1	1.0, 4.5	2.3	0.9, 5.8
Social functioning	6.2	2.6, 14.6	8.7	2.7, 28.5
School functioning	2.7	1.5, 5.0	3.1	1.4, 7.2

[a] Adjusted for age and gender

Discussion

Although the average parent-reported quality of life scores for adolescents with CHD in our sibling comparison were comparable to those reported in the normative population, they scored significantly lower than their unaffected siblings. This suggests that the presence of a CHD reduces the quality of life of affected adolescents. Additionally, uncontrolled confounding from familial characteristics such as SES may account for apparent similarities between those with CHD in the sibling group and the normative population and higher quality of life in the unaffected siblings compared with the normative estimates. To our knowledge, this is the first study to compare quality of life between sibling pairs or report quality of life measures in members of the family outside of the child with CHD and the parents.

Our findings from the sibling comparison agree with other studies that found lower quality of life in adolescents with CHD.[81,122] One large study also found that the largest deficit for affected adolescents was in school functioning and found no difference in emotional functioning.[122] School difficulties have been noted for patients with CHD including lower scores on standardized tests and greater use of special education services than healthy peers.[48,131] A couple of studies have found similar or higher quality of life in those with CHD, but these did not account for differences other than age and gender between the groups.[82,123] Therefore, the results of these studies may be susceptible to confounding by family characteristics similar to our comparison with the normative sample.

Differences between sibling pairs were seen in all CHD severity groups, but these differences were much more pronounced for those with the most severe forms of CHD. These findings are consistent with some other studies that found lower quality of life in those with more complex CHD,[81,83,87,122] although not all studies have observed an association with defect severity.[132,133] The effect of having a CHD was not meaningfully different for those with noncritical compared with those with critical two ventricle. Some studies have found higher quality of life in those with transition of the great arteries which may be raising the average for the critical two ventricle group.[65,134] More likely though, these two groups could appear similar because other characteristics, such as social support and comorbid conditions, are more strongly associated with quality of life than defect severity.[132,135,136]

Despite its findings, there are several limitations of this study that should be considered. Although using siblings as a comparison group adjusts for shared family factors that are confounders, it may actually dampen the true effect of CHD if having a

child with a chronic condition impacts the quality of life of all children in the family. We cannot fully assess this in our study without a healthy nonrelated group, but the siblings in our study had higher quality of life scores than expected from the normative population. Some have suggested the presence of a child with a chronic condition can bring a family closer which seems congruent with our findings.[137] However, as mentioned above, this higher quality of life in the siblings may simply reflect differences in confounding covariates between our sample and the normative population.

Although we can somewhat control for parent perception, we cannot exclude the possibility that at least part of the difference we observed is due to parents perceiving their child with CHD to have lower quality of life because of their health history instead of their actual functionality. The parent may also be more overprotective with their child with CHD which has been negatively associated with child quality of life.[128] Related to this, parents may over report good quality of life in the unaffected sibling because they have not had to experience the difficulties of having a birth defect.

Another limitation related to using sibling comparisons is whether these results are generalizable to the rest of the CHD population. Less than half of the families in our study had an eligible sibling and these families are likely different than those who did not. For example, the parents of those with an eligible sibling had higher incomes, more education, and were more likely to be non-Hispanic white than the full sample of participants. We also observed lower quality of life scores in our full sample of CHD compared with those with a sibling. Limiting to sibling pairs reduced our sample size which became problematic when we tried to stratify the conditional logistic regression analysis by severity and birth order. This is also related to our low response rate of only

32% which primarily stemmed from difficulty in locating families because we tried to recruit outside the clinic setting. We did not observe a difference in our estimates of low quality of life when we tried to adjust for differences between responders and nonresponders. However, we cannot eliminate the possibility that we did not observe a meaningful change because we did not have information on an important covariate for the full baseline cohort.

Conclusion

This study uses a sibling comparison group to suggest that the presence of a CHD reduces quality of life in adolescents and that this effect may be stronger in those with single ventricle CHD. Clinicians should be aware of this and monitor patients as they age for such deficits. Future research should examine potential interventions for children with CHD and their families to ensure that quality of life is optimized. Additionally, researchers assessing this outcome should be careful to address family characteristics such as SES in their analyses and interpretation.

CHAPTER 4. SELF-ESTEEM AND SELF-REPORTED QUALITY OF LIFE IN ADOLESCENTS WITH CONGENITAL HEART DISEASE

Introduction

Congenital heart disease (CHD) is the most common type of birth defect affecting almost 1% of births in the United States.[1,2] Advancements in treatment over the last several decades have dramatically improved the survival rate in these patients so that, currently, an estimated 85-90% reach adulthood.[4,98] Additionally, one study estimated that the median age of patients with CHD increased from 11 years in 1985 to 17 years in 2000 and that this age is likely to continue increasing.[116] This shift in the age of survivors necessitates research on the long term impacts of this condition and its treatments.

One potential impact of CHD is on self-perception, also considered self-esteem or self-worth. Self-perception is a multi-dimensional measure of how competent individuals perceive themselves.[70,138] Adolescence is an important developmental stage in the formation of self-perception as individuals begin to think more abstractly about themselves. Increased academic and social challenges also force teens to compare themselves to others and better understand their own capabilities.[139] Self-esteem could be reduced in those with CHD, especially those with more severe forms, because they may have real or perceived exercise restrictions that lead to limited involvement in sports, inadequate physical activity, and obesity.[94,117-119] These may also lead to a feeling of exclusion if the children with CHD cannot participate in the same activities as their peers. The presence of scars and other physical differences may also affect body image.[140,141] Finally, teens with CHD are also at increased risk for academic difficulties and lower social cognition which may also affect self-esteem.[48,100,131] However, other evidence

suggests those with CHD tend to have a strong sense of coherence and perceive themselves as normal making the relationship between CHD and self-esteem less clear.[88,90,140] It is important to understand whether self-perception is reduced in this population because low self-esteem has been shown to increase the risk for anxiety, depression, substance abuse, criminal behavior, and lower educational attainment in other populations.[139]

Another related outcome is quality of life which considers more than the physical morbidity of a chronic condition by combining it with an individual's perception of psychological and social functioning.[120] The potential differences related to CHD named above, including differences in physical appearance, exercise restriction, and academic difficulties, along with the increased risk for cognitive deficits compared with healthy peers and medication needs may reduce quality of life for those affected.[28,100] Evidence from studies using parent-reported quality of life has been mixed and less research has evaluated child-reported quality of life.[100,124,135] It has also been demonstrated that parent-report does not always correlate well with child-report.[122,133] Therefore, it is important to examine self-reported quality of life in order to better understand how these adolescents perceive limitations in their daily lives.

Thus far, few studies have assessed self-perception and self-reported quality of life in adolescents with CHD. Those studies that have included these outcomes, particularly those that have evaluated self-report in this age group, have had small sample sizes and mostly been convenience samples which may limit the ability to detect associations and limit the generalizability of their findings. The purpose of this study is to describe self-perception and self-reported quality of life in a cohort of adolescents

surgically treated for CHD to characterize the impact of CHD on their daily lives. We also assessed differences in these outcomes by CHD severity and conducted an exploratory analysis into factors related to self-reported quality of life including self-esteem.

Methods

The cohort was defined as all children born between 1998 and 2003 who were surgically treated for CHD at Children's Healthcare of Atlanta (CHOA). CHOA treats almost all cases of CHD in Georgia. Information on surgeries related to CHD treatment, mortality information, and contact information were obtained from CHOA clinical records. We obtained updated contact information by linking the parent or guardian of each child to current addresses and telephone numbers using Accurint, a commercial company that provides contact information from sources like credit cards, because children may not have been seen recently in CHOA facilities. Parent- and child-report were obtained from mailed questionnaires sent to eligible families.

Children were excluded if they were known to be deceased, had inadequate contact information, or their parents could not complete the questionnaires in English. We also excluded those with certain syndromes related to the outcomes of interest including 22q 11.2 deletion, Down, Holt-Oram, Loeys-Dietz, Triple X, Trisomy 18, Turner, VACTERL, and William's because the impact of these syndromes on quality of life would likely be greater than any potential impact from the CHD and its treatments. For this analysis we excluded those whose parent reported that the child was mentally or physically unable to complete the child questionnaire on their own.

Self-perception

The adolescents with CHD completed the Harter Self-Perception Profile questions for children (grades 3 – 8) and teens (grades 9 – 12) measuring global self-worth (self-esteem), behavioral conduct, close friendship, romantic appeal, and job competence. Although participants were asked questions in all of these scales, romantic appeal, close friendship, and job competence are only applicable for teens and therefore scores will only be reported for those in the relevant grade levels. This instrument also measures self-perception of scholastic competence, social competence, athletic competence, and physical appearance, but these were not included to minimize the length of the child questionnaire and because of the similarity of these questions to others in the quality of life instrument. For each item, the instrument instructs the child to pick which of two scenarios best describes themselves, and then whether the scenario they picked is "really true for me" or "sort of true for me". These options are given a score between 1 and 4 with 4 representing the most positive or competent self-description. Scores are then averaged over the items in each scale.[70,138]

Quality of life

The questionnaire for the adolescents also included the Pediatric Quality of Life Inventory (PedsQL), Version 4.0 which is a well-validated instrument designed to measure health-related quality of life at various ages.[129,130] The generic core for children (8 – 12 years old) and teens (13 – 18 years old) includes physical functioning, emotional functioning, social functioning, and school functioning. The cardiac module was also included which measures aspects of quality of life directly relevant for children with heart conditions including symptoms, perceived physical appearance, treatment anxiety,

cognitive problems, communication, and another treatment barriers section for children currently taking heart medication.[142] Each item in both the generic core and cardiac module is ranked by the respondent on a Likert scale from 'never a problem' to 'always a problem'. Responses are then transformed to a scale of 0 to 100, and these scores are averaged across items for each scale. Higher scores indicate better quality of life. Psychosocial health is the average of items in the emotional, social, and school functioning scales. These scales and physical health are averaged for the total score. Cutpoints for clinically relevant reduced quality of life for scales in the generic core have been identified from application of the PedsQL in a large normative population of healthy children and teens and those with various chronic conditions. These cutpoints represent one standard deviation below the population mean in the normative sample.[129]

Covariates

Diagnoses and treatment information from clinical records were used to categorize each child's CHD into three levels of severity. Critical single ventricle CHD represents the most severe forms including hypoplastic left heart syndrome and other single ventricle diagnoses that require the Fontan circulation. Children were classified as having critical two ventricle CHD if they had other forms of critical CHD that require treatment in the first year of life. These include coarctation of the aorta, critical aortic valve stenosis, critical pulmonary valve stenosis, d-transposition of the great arteries, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, and truncus arteriosus. The remaining forms of CHD were classified as noncritical and considered least severe. These included ventricular and atrial septal defects among others.[4]

Clinical records were supplemented by parent report to obtain the number of surgeries undergone by the child related to their CHD. Both sources were used because not all children may have remained at CHOA throughout their entire treatment and therefore the clinical records alone seemed to underreport the number of surgeries for some children. All other demographic and clinical characteristics were obtained from parent-report in the returned questionnaire. To assess the presence of other comorbidities, parents were asked if they had ever been told their child had a learning disability, attention deficit disorder (ADD) or attention deficit hyperactive disorder (ADHD), autism, intellectual disability, cerebral palsy, speech and language problems, asthma, diabetes, hearing problems, vision problems that cannot be corrected by glasses or contacts, or another type of disability. Each child was considered to have a comorbidity if their parent indicated at least one of these conditions and that the child currently had the condition. Examples of other disabilities listed by the parent include anxiety disorders, specific learning disabilities, Tourette's syndrome, and traumatic brain injury. Parents also reported their child's participation in after-school activities by ranking their involvement in specific activities on a Likert scale from "never" to "very often".

Analysis

Means were compared between the sample of adolescents with CHD and normative samples for each instrument using one sample t tests. Normative means for the Harter self-perception profile are provided separately by gender for each grade level, except twelfth grade, so to compare with our sample we combined these estimates using standardization so that it would reflect the gender and grade distribution in our study

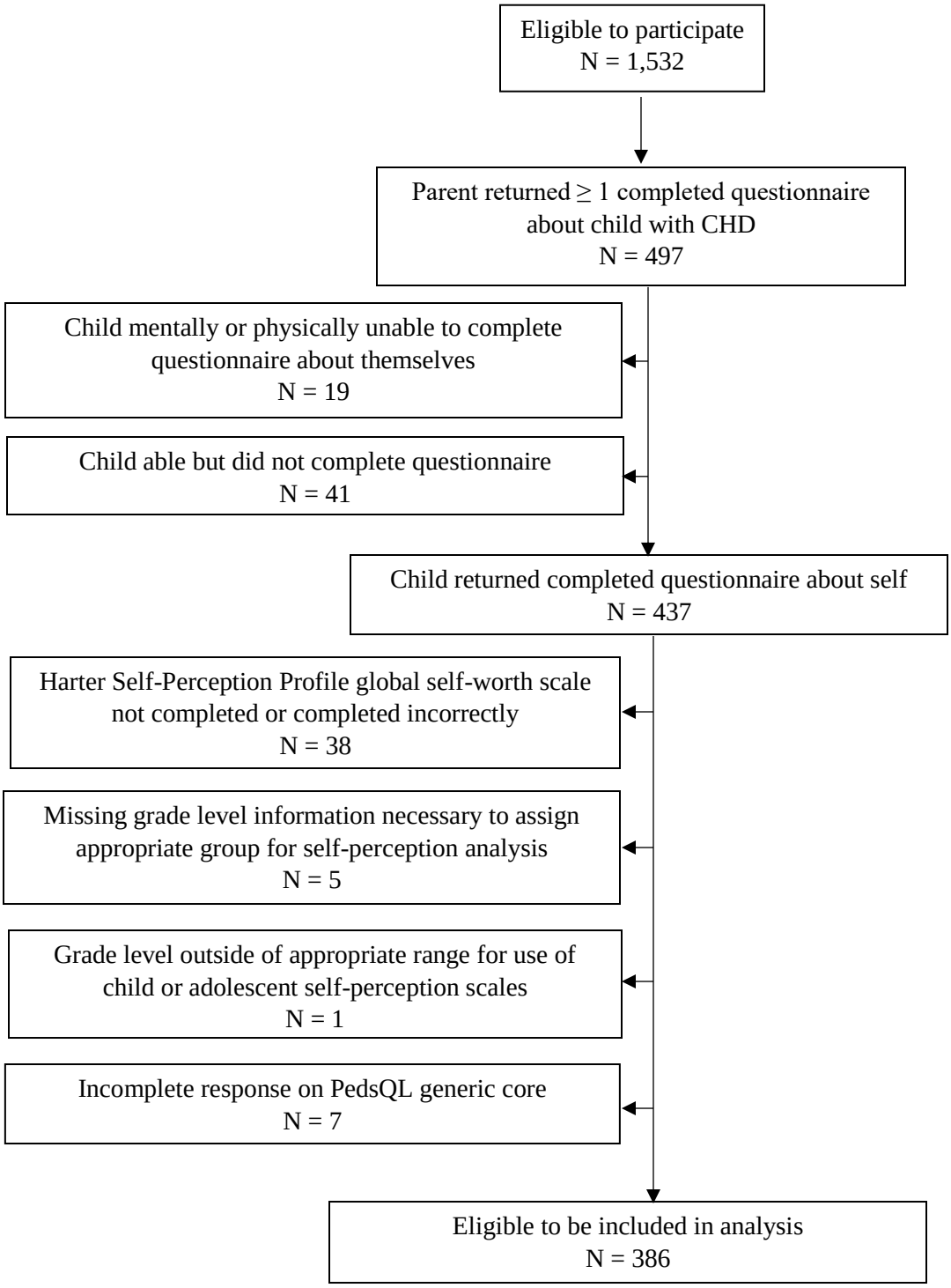
sample. Normative means for eleventh grade were used to represent eleventh and twelfth grade. When multiple normative samples were available for a grade level we used the most recent.[70,138] The proportion of adolescents with reported quality of life below the cutpoints on the PedsQL generic core were compared with the normative sample using the binomial distribution. To examine any differences in quality of life and self-perception between types of CHD these measures were compared between the three CHD severity groups using F tests (means), Kruskal-Wallis tests (medians), and chi-squared tests (proportion below cutpoint).

For quality of life we assessed clinical and demographic characteristics associated with reporting quality of life below the cutpoints in the composite scores: total quality of life, physical health, and psychosocial health. The prevalence of those below the cutpoints were compared between levels of each characteristic in a separate unadjusted model. Then, the clinical and demographic characteristics significantly related to low quality of life were evaluated together in an adjusted model. We also considered a third set of models in which self-esteem and participation in after-school activities, including sports and clubs, were included. These additional factors have been hypothesized to affect quality of life in previous studies,[78,143,144] but, as we cannot determine temporality in our study, it is possible that these factors are influenced by quality of life so we did not include these factors in the first regression analysis. Crude and adjusted prevalence ratios and 95% confidence intervals were estimated using log binomial regression models. When these models failed to converge we used a poisson model with a robust variance estimator as had been recommended.[145]

Results

Of the 1532 eligible adolescents with CHD we attempted to contact, 497 (32%) parents returned a completed questionnaire about their child with CHD. From parent report, 96% (N = 478) of these adolescents were able to complete the questionnaire about themselves. Eighty-eight percent (N = 437) returned a completed child questionnaire. After excluding adolescents who did not complete enough items on the global self-worth scale or completed this section incorrectly, those who were missing grade level information or were below third grade, for which the self-perception questions are not appropriate, and those missing too many items to calculate a total score on the PedsQL, 386 adolescents were included in this analysis (Figure 4.1).

Figure 4.1. Flow chart of the eligible sample for the analysis of self-perception and child-reported quality of life in adolescents with CHD



Demographic and clinical characteristics of the adolescents and their parents are shown in Table 4.1. The adolescents included in this analysis were 55% male, with a median age of 14 (range = 11 – 18) at the time of the survey, and the majority were non-Hispanic white. Almost half, 47%, had noncritical CHD, 36% were classified as critical two ventricle, and 17% as critical single ventricle. Biological mothers completed the majority of the parent questionnaires. This group of children was not meaningfully different than the original group of 497 adolescents with CHD whose parent participated (Table 4.1).

Table 4.1. Characteristics of adolescents with CHD who participated in this study compared with the full group for whom a parent returned a completed questionnaire

		Adolescent participants	Parent responders
Demographic characteristics		**N = 386**	**N = 497**
Age at survey	**Mean (SD)**	14.5 (1.7)	14.6 (1.7)
	Median (Range)	14 (11 - 17)	14 (11 - 18)
Grade level	**Mean (SD)**	8.6 (1.7)	8.5 (1.8)
	Median (Range)	8 (5 - 12)	8 (1 - 12)
	Missing	0	**7**
Gender	**Male**	209 (54%)	270 (54%)
Race/ethnicity	**Non-Hispanic white**	261 (68%)	316 (65%)
	Non-Hispanic black	76 (20%)	109 (22%)
	Hispanic	22 (6%)	34 (7%)
	Other	25 (7%)	30 (6%)
	Missing	2	8
Clinical characteristics			
Type of CHD	**Critical single ventricle**	67 (17%)	85 (17%)
	Critical 2 ventricle	133 (34%)	177 (36%)
	Noncritical	186 (48%)	235 (47%)
Number of surgeries	**1**	219 (57%)	290 (58%)
	2	66 (17%)	80 (16%)
	3	60 (16%)	74 (15%)

	4+	41 (11%)	53 (11%)
Comorbid condition	**Yes**	179 (46%)	241 (48%)
Current use of heart medication	**Yes**	118 (31%)	145 (30%)
Current use of medication for other condition	**Yes**	131 (34%)	167 (34%)
Social characteristics			
Time spent with friends outside of school	**Fairly or very often**	208 (54%)	268 (55%)
	Sometimes	117 (31%)	141 (29%)
	Never or almost never	57 (15%)	82 (17%)
	Missing	4	6
Participation in sports or on a sports team	**Fairly or very often**	160 (42%)	200 (41%)
	Sometimes	54 (14%)	72 (15%)
	Never or almost never	169 (44%)	220 (45%)
	Missing	3	5
Participation in club or organization	**Fairly or very often**	217 (57%)	258 (52%)
	Sometimes	72 (19%)	102 (21%)
	Never or almost never	94 (25%)	132 (27%)
	Missing	3	5
Participation in artistic activity	**Fairly or very often**	152 (40%)	190 (39%)
	Sometimes	59 (15%)	75 (15%)
	Never or almost never	170 (45%)	224 (46%)
	Missing	5	8
Characteristics of the parent responder			
Relation to child with CHD	**Biological mother**	331 (86%)	413 (84%)
	Biological father	38 (10%)	57 (12%)
	Grandmother	4 (1%)	7 (1%)
	Other	12 (3%)	12 (2%)
	Missing	1	8
Highest level of education	**< High school diploma/GED**	26 (7%)	43 (9%)
	High school diploma/GED - some college	153 (40%)	206 (42%)
	4 year college degree	119 (31%)	143 (29%)
	> 4 year college degree	85 (22%)	95 (20%)
	Missing	3	10

	< $25,000	60 (16%)	91 (19%)
Annual household income	**$25,000 - $50,000**	67 (18%)	88 (18%)
	$50,000 - $100,000	115 (31%)	142 (30%)
	>$100,000	131 (35%)	156 (33%)
	Missing	13	20
Marital status	**Married**	290 (75%)	353 (72%)
	Living with partner	5 (1%)	7 (1)%
	Divorced, separated, widowed	63 (16%)	94 (19%)
	Never married	27 (7%)	36 (7%)
	Missing	1	7

Self-perception

The adolescents with CHD reported the most positive self-perception in global self-worth and the least positive in romantic appeal. Romantic appeal was also the least positive in the normative sample. Compared with the standardized normative means, the adolescents with CHD reported more positive self-worth (CHD mean = 3.2; normative mean = 2.9), behavioral conduct (CHD mean = 3.2; normative mean = 2.9), and romantic appeal (CHD mean = 2.7; normative mean = 2.5). Those with CHD reported lower, more negative, job competence (CHD mean = 3.0; normative mean = 3.2), and there was no difference in close friendship. Among adolescents with CHD, females reported lower self-worth but more positive behavioral conduct than males (Table 4.2). There were small decreases in all scales of self-perception with increasing severity of CHD but these differences were not meaningfully different (Table 4.3).

Table 4.2. Self-perception as measured on the Harter Self-Perception Profile for adolescents with CHD compared with normative means standardized to the CHD population on gender and grade level

	Standardized normative sample	**Adolescents with CHD**			
	Mean	**N**	**Mean (SD)**	**Median (IQR)**	**P-value[1]**
Global self worth	*2.90*	386	3.19 (0.73)	3.4 (2.8 - 3.8)	<0.01
Behavioral conduct	*2.87*	384	3.19 (0.65)	3.2 (2.8 - 3.8)	<0.01
Close friendship	*3.16*	186	3.09 (0.74)	3.2 (2.6 - 3.8)	0.19
Job competence	*3.22*	182	2.97 (0.64)	3.0 (2.6, 3.4)	<0.01
Romantic appeal	*2.53*	176	2.73 (0.72)	2.8 (2.2, 3.2)	<0.01

[1]Means compared using a one sample t test

Table 4.3. Self-perception compared between the three levels of CHD severity

	Noncritical			Critical 2 ventricle			Critical single ventricle				
	N	**Mean (SD)**	**Median (IQR)**	**N**	**Mean (SD)**	**Median (IQR)**	**N**	**Mean (SD)**	**Median (IQR)**	**P-value[1]**	**P-value[2]**
Global self worth	186	3.22 (0.73)	3.4 (2.75, 3.80)	133	3.19 (0.70)	3.40 (2.8, 3.8)	67	3.09 (0.80)	3.2 (2.6, 3.8)	0.46	0.57
Behavioral conduct	186	3.22 (0.63)	3.4 (2.8, 3.8)	132	3.17 (0.67)	3.2 (2.8, 3.8)	66	3.11 (0.64)	3.2 (2.6, 3.6)	0.48	0.45
Close friendship	91	3.13 (0.73)	3.2 (2.8, 3.8)	69	3.14 (0.72)	3.2 (2.8, 3.6)	26	2.82 (0.83)	2.6 (2.2, 3.6)	0.13	0.14
Romatic appeal	89	2.84 (0.72)	3.0 (2.4, 3.4)	62	2.63 (0.69)	2.8 (2.2, 3.0)	25	2.55 (0.72)	2.4 (2.0, 3.0)	0.09	0.07
Job competence	89	3.02 (0.59)	3.0 (2.6, 3.6)	68	2.96 (0.73)	3.0 (2.6, 3.4)	25	2.86 (0.62)	3.0 (2.4, 3.4)	0.54	0.59

[1]Means compared between the three groups using an f

[2]Medians compared using the Kruskal-Wallis tests

Quality of life

In the generic core scales, those with CHD reported the lowest quality of life in school functioning and highest in social functioning (medians = 75.0 and 85.0 respectively). This was different from the pattern in the normative sample in which scores are highest in physical health and lowest in emotional functioning. Those with CHD had lower self-reported quality of life compared with the normative sample in the total score (CHD mean = 78.6, normative mean = 82.9), physical health (CHD mean = 81.3, normative mean = 86.9), psychosocial health (CHD mean = 77.2, normative mean = 80.7), and school functioning (CHD mean = 71.6, normative mean = 79.9). Among the scales from the cardiac module, the adolescents with CHD reported the highest scores for treatment anxiety and lowest in cognitive problems (medians = 79.1 and 69.6 respectively). Reported quality of life in all scales decreased with increased CHD severity but differences in medians were only statistically significantly different between groups for physical health and symptoms (Table 4.4).

Table 4.4. Self-reported quality of life as measured by the PedsQL, version 4.0 generic core and cardiac module compared between adolescents with CHD and normative means and compared by CHD severity among the affected adolescents

		Normative sample	Self-report	p-value[1]	Noncritical	Critical 2 ventricle	Criticle single ventricle	p-value[2]
Generic Core		***Child report***	**N = 386**		**N = 186**	**N = 133**	**N = 67**	
Total	**Mean (SD)**	*82.9 (13.2)*	78.6 (16.6)	<0.01	82.4 (14.9)	77.9 (16.6)	69.8 (17.8)	0.06
	Median (IQR)		81.5 (69.6, 91.3)		84.8 (73.9, 93.5)	81.5 (67.4, 90.2)	73.9 (59.8, 82.6)	0.07
Physical health[3]	**Mean (SD)**	*86.9 (13.9)*	81.3 (18.3)	<0.01	85.5 (15.9)	81.4 (18.8)	69.5 (18.8)	0.01
	Median (IQR)		84.4 (68.8, 96.9)		90.6 (75.0, 100)	87.5 (68.8, 96.9)	71.9 (62.5, 81.3)	<0.01
	Missing		1		1	0	0	
Psychosocial health	**Mean (SD)**	*80.7 (14.7)*	77.2 (17.8)	<0.01	80.7 (16.5)	76.0 (17.7)	69.9 (19.4)	0.23
	Median (IQR)		81.7 (65.0, 90.0)		85.0 (71.7, 93.3)	80.0 (63.3, 90.0)	71.7 (58.3, 86.7)	0.31
Emotional functioning	**Mean (SD)**	*78.2 (18.6)*	77.5 (21.6)	0.53	80.2 (21.0)	76.3 (21.4)	72.5 (22.7)	0.63
	Median (IQR)		80.0 (60.0, 100.0)		85.0 (65.0, 100)	80.0 (65.0, 95.0)	80.0 (55.0, 90.0)	0.67
Social functioning	**Mean (SD)**	*84.0 (17.4)*	82.4 (19.0)	0.09	86.2 (16.1)	81.6 (19.8)	73.4 (21.6)	0.02
	Median (IQR)		85.0 (75.0, 100.0)		90.0 (75.0, 100)	90.0 (70.0, 100)	75.0 (60.0, 90.0)	0.08
School functioning	**Mean (SD)**	*79.9 (16.9)*	71.6 (21.5)	<0.01	75.7 (20.3)	70.0 (21.4)	63.7 (22.5)	0.65
	Median (IQR)		75.0 (60.0, 90.0)		80.0 (60.0, 95.0)	70.0 (55.0, 90.0)	70.0 (50.0, 80.0)	0.75
Cardiac module								
Symptoms	**Mean (SD)**	-	76.6 (19.1)	-	80.5 (17.3)	77.5 (19.0)	64.0 (19.0)	0.09

	Median (IQR)		78.6 (64.3, 92.9)		84.5 (71.4, 92.9)	80.4 (67.9, 92.9)	60.7 (53.6, 78.6)	0.01
	Missing		1		0	1	0	
Physical appearance	**Mean (SD)**	-	75.9 (28.2)	-	77.1 (28.0)	76.0 (28.9)	72.3 (27.9)	0.52
	Median (IQR)		83.3 (58.3, 100)		91.7 (58.3, 100)	83.3 (66.7, 100)	83.3 (50.0, 100)	0.55
	Missing		2		1	1	0	
Treatment anxiety	**Mean (SD)**	-	79.1 (25.8)	-	83.1 (24.0)	76.9 (26.4)	72.3 (28.0)	0.86
	Median (IQR)		93.8 (62.5, 100)		100 (68.8, 100)	87.5 (56.3, 100)	81.3 (50.0, 100)	0.59
	Missing		2		1	1	0	
Cognitive problems	**Mean (SD)**	-	69.6 (24.3)	-	73.9 (22.9)	68.1 (25.3)	61.2 (23.8)	0.56
	Median (IQR)		70.0 (55.0, 90.0)		75.0 (60.0, 95.0)	70.0 (50.0, 90.0)	65.0 (45.0, 85.0)	0.42
	Missing		1		1	0	0	
Communication	**Mean (SD)**	-	76.4 (26.5)	-	79.5 (24.6)	76.1 (28.3)	68.3 (26.9)	0.19
	Median (IQR)		83.3 (66.7, 100)		83.3 (66.7, 100)	83.3 (66.7, 100)	66.7 (50.0, 91.7)	0.10
	Missing		2		2	0	0	

[1]One sample t test comparing means in adolescents with CHD to normative sample
[2]Comparison between three CHD severity groups using f tests (means) and Kruskal-Wallis tests (medians)

Table 4.5 presents the proportion of adolescents with self-reported quality of life more than one standard deviation below the normative mean. A greater proportion of those with noncritical CHD had self-reported low quality of life than expected based on the normative sample in physical health (noncritical CHD = 20.5%, 95% CI: 14.7 - 26.4%; normative sample = 14.8) and school functioning (noncritical CHD = 25.3%, 95% CI: 19.0 – 31.5; normative sample = 17.0). The proportions with low quality of life in those with critical two ventricle CHD and critical single ventricle were greater than the normative sample in all scales. In fact, in the group with critical single ventricle, 55% (95% CI: 43.3 – 67.1%) reported low physical health and 40% (95% CI: 28.6 – 50.0) reported low psychosocial health (Table 4.5).

Table 4.5. Prevalence of adolescents with self-reported quality of life below the cutpoint of 1 standard deviation below the normative mean

	Normative sample	**Adolescents with CHD (N=386)**	**p-value[1]**	**Noncritical (N=186)**	**Critical 2 ventricle (N=133)**	**Criticle single ventricle (N=67)**	**p-value[2]**
Generic Core	*%*	% (95% CI)		% (95% CI)	% (95% CI)	% (95% CI)	
Total	*16.9*	25.9 (21.5, 30.3)	<0.01	18.3 (12.7, 23.8)	27.8 (20.2, 35.4)	43.3 (31.4, 55.2)	<0.01
Physical health	*14.8*	28.3 (23.8, 32.8)	<0.01	20.5 (14.7, 26.4)	25.6 (18.2, 33.0)	55.2 (43.3, 67.1)	<0.01
Psychosocial health	*15.8*	25.9 (21.5, 30.3)	<0.01	19.9 (14.2, 25.6)	27.1 (19.5, 34.6)	40.3 (28.6, 52.0)	<0.01
Emotional functioning	*14.2*	21.0 (16.9, 25.1)	<0.01	17.7 (12.3, 23.2)	22.6 (15.5, 29.7)	26.9 (16.8, 39.1)	0.25
Social functioning	*15.9*	18.9 (15.0, 22.8)	0.11	11.3 (6.7, 16.7)	22.6 (15.5, 29.7)	32.8 (21.6, 44.1)	<0.01
School functioning	*17.0*	32.4 (27.7, 37.1)	<0.01	25.3 (19.0, 31.5)	39.1 (30.8, 47.4)	38.8 (27.1, 50.5)	0.02

[1]Prevalence compared between all adolescents with CHD and the normative sample using the binomial distribution

[2]Prevalence compared between the three CHD severity groups using chi-squared tests

In the unadjusted analysis, CHD severity was associated with low total quality of life, physical health, and psychosocial health along with female gender, low household income, lower parent education (only for total quality of life and psychosocial health), increased number of surgeries related to CHD, heart medication use, medication use for another condition, and the presence of a comorbidity. After adjustment for the other factors just listed, the associations between low quality of life and CHD severity were generally unchanged for critical two ventricle CHD but were attenuated for critical single ventricle (Tables 4.6-4.8). Critical two ventricle CHD was associated with approximately a 50% greater prevalence of low total quality of life compared with noncritical CHD (adj. PR = 1.5, 95% CI: 1.0 – 2.3). Female gender also remained associated with low total quality of life along with the lowest income group, and undergoing four or more cardiac surgeries (Table 4.6). Low physical health remained associated with female gender and the presence of a comorbidity. Lower income and more cardiac surgeries also appeared to be somewhat related but trends were not as clear after adjustment (Table 4.7). Again, female gender and increased number of surgeries related to CHD were predictive of low reported psychosocial health in addition to the use of medication for a condition other than CHD (Table 4.8).

Table 4.6. Regression analysis to assess the association between characteristics and low total self-reported quality of life (> 1 SD below normative mean) among adolescents with CHD

Total quality of life < 1 SD below normative mean: N = 100, 25.9%		Unadjusted			Model 1			Model 2		
		PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Demographic characteristics										
Age	1 year	0.97	0.88, 1.08	0.622						
Gender	Male	ref			ref			ref		
	Female	1.57	1.11, 2.20	**0.01**	1.57	1.12, 2.21	**0.01**	1.29	0.91, 1.83	0.15
Race	Non-Hispanic white	ref		0.98						
	Non-Hispanic black	1.01	0.66, 1.55							
	Hispanic	0.87	0.39, 1.94							
	Other	1.07	0.55, 2.08							
Family income	< $25,000	1.92	1.18, 3.12	**0.04**	1.74	1.08, 2.81	0.10	1.35	0.81, 2.25	0.28
	$25,000 - $50,000	1.72	1.05, 2.81		1.57	0.99, 2.49		1.59	0.99, 2.53	
	$50,000 - $100,000	1.28	0.79, 2.06		1.24	0.79, 1.95		1.36	0.85, 2.18	
	>$100,000	ref			ref			ref		
Parent education	< High school diploma/GED	1.47	0.48, 1.40	0.10						
	High school diploma/GED - some college	1.33	0.85, 2.09							
	4 year college degree	0.82	0.77, 2.82							

	> 4 year college degree	ref								
Family characteristics										
Family structure	Only child	ref								
	At least 1 sibling	1.00	0.67, 1.49	0.98						
Birth order (among those with a sibling)	1st	ref		0.69						
	2nd	1.27	0.84, 1.91							
	3rd	1.04	0.51, 2.12							
	4th +	0.95	0.27, 3.36							
Clinicial characteristics										
CHD severity	Noncritical	ref		**<0.01**	ref			ref		0.13
	Critical 2 ventricle	1.52	1.01, 2.29		1.54	1.03, 2.31	0.10	1.41	0.96, 2.09	
	Critical 1 ventricle	2.37	1.57, 3.57		1.10	0.65, 1.88		0.98	0.58, 1.66	
Number of heart surgeries (parent and medical records)	1	ref		**<0.01**	ref			ref		0.21
	2	1.33	0.80, 2.21		1.12	0.68, 1.84	0.17	0.98	0.61, 1.58	
	3	2.28	1.51, 3.44		1.60	0.95, 2.69		1.63	1.01, 2.65	
	4+	2.54	1.65, 3.91		2.00	1.16, 3.45		1.46	0.86, 2.49	
	No	ref			ref			ref		

Medication use (for CHD)	Yes	2.11	1.52, 2.94	**<0.01**	1.28	0.82, 1.99	0.28	1.31	0.87, 1.95	0.19
Medication use (for other conditions)	No	ref			ref			ref		
	Yes	1.88	1.35, 2.62	**<0.01**	1.38	0.93, 2.05	0.11	1.14	0.81, 1.61	0.45
Presence of a comorbidity	No	ref			ref			ref		
	Yes	1.73	1.23, 2.45	**<0.01**	1.06	0.69, 1.61	0.79	1.41	0.96, 2.08	0.08
Self-percption										
Global self-worth	1 SD increase	0.64	0.58, 0.70	**<0.01**				0.65	0.56, 0.75	**<0.01**
After school activities										
Participation in sports	Fairly of very often	ref						ref		
	Sometimes	2.09	1.07, 4.09	**<0.01**				1.69	0.86, 3.31	**0.01**
	Never, almost never	3.90	2.40, 6.32					2.06	1.23, 3.46	
Participation in club or organization	Fairly of very often	ref		**<0.01**				ref		
	Sometimes	1.51	0.95, 2.40					1.00	0.62, 1.62	0.78
	Never, almost never	2.25	1.56, 3.25					1.15	0.75, 1.76	
	Fairly of very often	ref		0.35						

Participation in artistic activity	Sometimes	0.86	0.48, 1.53			
	Never, almost never	1.22	0.84, 1.76			
Spend time with friends outside of school	Fairly of very often	ref		0.11		
	Sometimes	1.42	0.98, 2.07			
	Never, almost never	1.46	0.92, 2.32			

Table 4.7. Regression analysis to assess the association between characteristics and low self-reported physical functioning (< 1 SD below normative mean) among adolescents with CHD

Physical functioning < 1 SD below normativ mean: N = 109, 28.3%		Unadjusted			Model 1			Model 2		
		PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Demographic characteristics										
Age	1 year	0.94	0.86, 1.04	0.21						
Gender	Male	ref			ref			ref		
	Female	1.87	1.35, 2.61	**<0.01**	1.84	1.32, 2.56	**<0.01**	1.58	1.14, 2.18	**0.01**
Race	Non-Hispanic white	ref		0.93						
	Non-Hispanic black	1.06	0.71, 1.59							
	Hispanic	1.17	0.61, 2.22							
	Other	1.17	0.64, 2.15							
Family income	< $25,000	1.66	1.04, 2.63	**0.04**	1.48	0.85, 2.58	0.22	1.32	0.74, 2.35	0.19
	$25,000 - $50,000	1.75	1.13, 2.72		1.73	1.07, 2.81		1.81	1.09, 3.02	
	$50,000 - $100,000	1.15	0.73, 1.80		1.25	0.81, 1.92		1.36	0.89, 2.08	
	>$100,000	ref			ref			ref		
Parent education	< High school diploma/GED	1.81	1.06, 3.09	0.20	1.21	0.62, 2.34	0.33	1.2	0.61, 2.35	0.15
	High school diploma/GED - some college	1.31	0.84, 2.05		0.76	0.46, 1.26		0.69	0.43, 1.12	
	4 year college degree	1.21	0.75, 1.95		0.95	0.59, 1.50		0.94	0.61, 1.45	
	> 4 year college degree	ref			ref			ref		

Family characteristics										
Family structure	Only child	ref								
	At least 1 sibling	0.91	0.63, 1.30	0.59						
Birth order (among those with a sibling)	1st	ref								
	2nd	1.42	0.95, 2.11	0.23						
	3rd	0.89	0.41, 1.93							
	4th +	1.91	0.86, 4.21							
Clinicial characteristics										
CHD severity	Noncritical	ref		**<0.01**	ref		0.28	ref		0.47
	Critical 2 ventricle	1.24	0.83, 1.87		1.23	0.82, 1.86		1.12	0.74, 1.70	
	Critical 1 ventricle	2.69	1.88, 3.84		1.52	0.88, 2.62		1.42	0.81, 2.47	
Number of heart surgeries (parent and medical records)	1	ref		**<0.01**	ref		0.20	ref		0.34
	2	1.65	1.04, 2.62		1.56	0.99, 2.47		1.46	0.92, 2.32	
	3	2.63	1.80, 3.86		1.52	0.86, 2.71		1.56	0.91, 2.68	
	4+	2.66	1.75, 4.05		1.72	0.95, 3.12		1.41	0.78, 2.53	
Medication use (for CHD)	No	ref			ref			ref		
	Yes	2.28	1.67, 3.11	**<0.01**	1.29	0.83, 2.00	0.26	1.30	0.85, 1.99	0.23
Medication use (for	No	ref			ref					
	Yes	1.64	1.19, 2.25	**<0.01**	1.11	0.76, 1.62	0.59	0.96	0.68, 1.38	0.84

other conditions)										
Presence of a comorbidity	No	ref			ref					
	Yes	1.72	1.24, 2.38	**<0.01**	1.56	1.06, 2.30	**0.02**	1.43	0.96, 2.12	0.08
Self-percption										
Global self-worth	1 SD increase	0.72	0.64, 0.81	**<0.01**				0.77	0.67, 0.89	**<0.01**
After school activities										
Participation in sports	Fairly of very often	ref		**<0.01**				ref		**0.01**
	Sometimes	2.06	1.12, 3.79					1.8	1.00, 3.27	
	Never, almost never	3.52	2.27, 5.50					2.11	1.29, 3.48	
Participation in club or organization	Fairly of very often	ref		**<0.01**				ref		0.78
	Sometimes	1.47	0.97, 2.25					1.09	0.69, 1.73	
	Never, almost never	1.89	1.32, 2.68					1.16	0.77, 1.73	
Participation in artistic activity	Fairly of very often	ref		0.32						
	Sometimes	0.7	0.40, 1.23							
	Never, almost never	1.04	0.74, 1.46							
Spend time with friends outside of school	Fairly of very often	ref		**0.03**				ref		0.62
	Sometimes	1.52	1.07, 2.15					1.12	0.77, 1.62	
	Never, almost never	1.55	1.01, 2.38					0.93	0.63, 1.37	

Table 4.8. Regression analysis to assess the association between characteristics and low self-reported psychosocial functioning (< 1 SD below normative mean) among adolescents with CHD

Psychosocial functioning < 1 SD below normative mean: N = 100, 25.9%		Unadjusted			Model 1			Model 2		
		PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
Demographic characteristics										
Age	1 year	0.98	0.88, 1.09	0.70						
Gender	Male	ref			ref			ref		
	Female	1.5	1.07, 2.11	**0.02**	1.65	1.17, 2.31	**<0.01**	1.23	0.88, 1.72	0.22
Race	Non-Hispanic white	ref		0.99						
	Non-Hispanic black	1.03	0.67, 1.57							
	Hispanic	1.06	0.52, 2.17							
	Other	1.09	0.56, 2.11							
Family income	< $25,000	2.01	1.29, 3.39	**<0.01**	1.68	0.91, 3.08	0.20	1.31	0.67, 2.54	0.42
	$25,000 - $50,000	1.96	1.21, 3.20		1.56	0.91, 2.66		1.64	0.91, 2.97	
	$50,000 - $100,000	1.19	0.72, 1.96		1.07	0.62, 1.86		1.24	0.71, 2.16	
	>$100,000	ref			ref			ref		
Parent education	< High school diploma/GED	1.55	0.80, 3.00	**0.02**	0.87	0.41, 1.86	0.07	0.84	0.41, 1.72	0.90
	High school diploma/GED - some college	1.46	0.93, 2.31		0.94	0.55, 1.58		0.81	0.47, 1.35	
	4 year college degree	0.79	0.45, 1.38		0.53	0.31, 0.94		0.53	0.32, 0.88	
	> 4 year college degree	ref			ref			ref		

Family characteristics										
Family structure	Only child	ref								
	At least 1 sibling	0.89	0.61, 1.31	0.56						
Birth order (among those with a sibling)	1st	ref		0.73						
	2nd	1.00	0.67, 1.51							
	3rd	0.66	0.28, 1.53							
	4th +	0.84	0.24, 2.96							
Clinicial characteristics										
CHD severity	Noncritical	ref		**0.01**	ref		0.27	ref		0.33
	Critical 2 ventricle	1.36	0.91, 2.03		1.37	0.92, 2.05		1.23	0.84, 1.79	
	Critical 1 ventricle	2.03	1.34, 3.05		1.03	0.62, 1.71		0.87	0.52, 1.44	
Number of heart surgeries (parent and medical records)	1	ref		**<0.01**	ref		0.18	ref		0.29
	2	1.34	0.82, 2.20		1.19	0.73, 1.95		1.03	0.63, 1.69	
	3	2.00	1.31, 3.04		1.66	1.01, 2.74		1.59	0.98, 2.59	
	4+	2.29	1.47, 3.55		1.91	1.11, 3.31		1.36	0.79, 2.35	
Medication use (for CHD)	No	ref			ref			ref		
	Yes	1.99	1.43, 2.77	**<0.01**	1.20	0.78, 1.84	0.41	1.28	0.85, 1.92	0.23
Medication use (for	No	ref						ref		
	Yes	2.00	1.43, 2.79	**<0.01**	1.72	1.17, 2.54	**0.01**	1.40	1.00, 1.96	**0.05**

other conditions)										
Presence of a comorbidity	No	ref						ref		
	Yes	1.66	1.18, 2.35	**<0.01**	1.14	0.78, 1.66	0.51	1.18	0.82, 1.70	0.38
Self-percption										
Global self-worth	1 SD increase	0.67	0.60, 0.75	**<0.01**				0.65	0.56, 0.76	**<0.01**
After school activities										
Participation in sports	Fairly of very often	ref		**<0.01**				ref		**<0.01**
	Sometimes	2.11	1.0, 4.48					1.50	0.72, 3.15	
	Never, almost never	5.07	2.99, 8.60					2.67	1.55, 4.63	
Participation in club or organization	Fairly of very often	ref		**<0.01**						
	Sometimes	1.71	1.08, 2.72					1.09	0.66, 1.81	0.89
	Never, almost never	2.56	1.76, 3.71					1.10	0.73, 1.67	
Participation in artistic activity	Fairly of very often	ref		0.34						
	Sometimes	1.17	0.69, 1.99							
	Never, almost never	1.33	0.90, 1.95							
Spend time with friends outside of school	Fairly of very often	ref		**<0.01**						0.81
	Sometimes	1.69	1.15, 2.47					1.14	0.77, 1.68	
	Never, almost never	1.92	1.23, 2.97					1.06	0.71, 1.58	

Increased self-worth was associated with better quality of life in all three composites scales. Among the after-school activities considered, less frequent participation in sports and clubs or organizations was associated with low total quality of life, physical health, and psychosocial health. Less time spent with friends was also associated with low physical health and psychosocial health. When these factors were included in the full model with the demographic and clinical characteristics, participation in clubs and time spent with friends was no longer meaningfully related to quality of life. However, self-worth and participation in sports remained the most strongly associated factors with low quality of life. Both factors were more strongly associated with psychosocial health than physical health (1 SD increase in self-worth adj. PR = 0.65 and 0.77 respectively; never or almost never vs. often participation in sports PR = 2.7 and 2.1 respectively) (Tables 6-8).

Discussion

This study found that the adolescents with CHD reported similar or even higher self-perceptions compared with healthy children, but a significantly larger proportion reported low quality of life. These adolescents may not see themselves as different despite recognizing their own limitations because they have lived with the heart condition their whole lives and therefore haven't experienced anything different. Adolescents with single ventricle CHD reported especially low quality of life in physical functioning, psychosocial functioning, and symptoms. However, after adjustment, other factors were more strongly related to physical and psychosocial functioning than CHD severity including family income, number of cardiac surgeries, self-esteem, and participation in sports.

Our findings of similar self-concept in adolescents and children with CHD compared with healthy children has been observed in previous research,[74,76,146] but several other studies have reported lower self-esteem in affected patients.[77,141] One study in Israel only found a difference between adolescents with severe CHD and healthy children.[144] Although we did not observe this finding, we did see slightly lower self-esteem in those with critical single ventricle CHD than in the other two severity groups. Similar to gender patterns observed in the normative samples,[138] we found lower self-worth in females with CHD than males. This is contrary to some findings in CHD populations that have observed lower self-worth in males,[77,141] but one study of adolescents and adults with single ventricle CHD did report lower body image and satisfaction with appearance in females compared males which is more congruent with our finding.[141]

Results from self-reported quality of life have been mixed, but generally concur with our findings of lower quality of life in affected individuals.[80,124,125,142] One of the larger studies to report such results found that 17% and 14% of teens reported physical functioning and psychosocial functioning more than one standard deviation below the normative mean.[122] These proportions are lower than what we observed, but this study included children with milder forms of CHD including those who did not require treatment and children with acquired heart disease. The same study also reported lower quality of life for those with single ventricle CHD compared with other severities in physical functioning, psychosocial functioning, and the symptoms scale on the cardiac module similar to our study. Nevertheless, this study and our own still observed differences between the least severe forms of CHD and healthy norms.[122] One potential

explanation for this difference in adolescents with mild CHD compared with unaffected adolescents is that parental stress or overprotection may force limitations on children even when it is not medically necessary.[146] Interestingly, we observed less of a difference in emotional functioning between CHD types which is similar to at least one other study.[81] Additionally, as we observed, previous research has found stronger associations between quality of life and clinical and demographic characteristics then with CHD severity.[125,135] These include socioeconomic status,[85,87] which we observed, as well as parental support,[63] and sense of coherence,[90] which were not assessed in this study.

In the exploratory analysis we also found that self-esteem and participation in sports were strongly related to physical and psychosocial functioning. One study assessing self-perception along with clinical and demographic characteristics found that self-perception accounted for the largest proportion of the variance in quality of life, 33%.[78] Studies of both healthy adolescents and those with CHD have hypothesized the importance of the impact of physical activity on self-esteem and quality of life through the formation of peer groups and feelings of inclusion that come with being part of a team.[143,147,148] Nevertheless, there is little research to examine this relationship with self-reported quality of life in the CHD population.[143,149] Some studies have assessed exercise capacity and found that it is related to physical but not psychosocial functioning,[65,150] but we would not expect exercise capacity to have the same social impact that participation in sports would because that does not equate to actual physical activity or involvement with teams. Although causality should not be inferred from our results, it is interesting to note that participation in clubs or organizations and increased time spent with friends were not

related to quality of life in our study after adjustment for other factors. Therefore, there may be other aspects of sports participation and exercise that are more important contributors to psychosocial health such as body image and confidence.

Strengths

This study benefits from self-reported outcomes on a fairly large, population-based sample of adolescents with CHD for which these outcomes were combined with clinical records and parent-reported information. Information was available on a number of clinical and demographic characteristics along with participation in certain after-school activities. To classify CHD severity, we had the advantage of using diagnoses and surgical information. This is ideal over using ICD-9 codes because some defects can be placed in two different categories depending on the severity of symptoms within the individual. The inclusion of the cardiac module along with the generic core scales for the PedsQL allowed us to assess other aspects of quality of life that may be more relevant to adolescents with CHD.

Limitations

There are several limitations that should be considered with this study. First, we did not collect self-esteem or self-reported quality of life from a healthy comparison group and therefore had to rely on comparison with normative samples. We tried to minimize differences between our population and the normative sample for the Harter self-perception profile by standardizing the means by gender and grade level. However, we were not able to make such adjustments for the PedsQL scores, and, for both

measures, we lacked information on other potentially important confounders such as socioeconomic status.

This study is cross-sectional so it did not allow us to examine causal associations between certain factors and quality of life because we are unable to establish temporality. Specifically, quality of life may impact self-esteem. Considering the relationship with this directionality, reporting low total quality of life would be associated with a 0.62 decrease in self-esteem which is almost equivalent to a one standard deviation reduction. Similarly, participation in sports may be a cause, result from, or act as a mediator of this relationship. Likely, these factors all affect each other over time as the child develops. We also lacked information on parental stress, parenting style, and other family characteristics which have been related to our outcomes of interest.

Finally, our results may not be generalizable to the entire population of adolescents surgically treated for CHD. Our baseline cohort may well represent this population because CHOA treats almost all CHD cases in the state of Georgia, and we tried to maintain this representativeness by not limiting our recruitment to those still being seen in these facilities. However, this led to difficulty in locating families and a response rate of only 32%. Additionally, 22% of the adolescents whose parent responded to our study did not have usable responses on the child questionnaire. As some of these adolescents were not able to participate or completed the instruments incorrectly, our sample may be healthier and have less difficulties compared with the entire population. There was a small increase in the proportion with comorbidities in the sample whose parent responded compared with the group of adolescents included in the analysis which may lend evidence to this point.

Conclusion

All adolescents surgically treated for CHD should be monitored for low quality of life. Although this prevalence is considerably larger in those with more severe forms of CHD, adjusted analyses suggests that other characteristics related to CHD severity are more directly associated with quality of life than the diagnosis alone. Future research should incorporate longitudinally collected data to better examine the causal relationships between clinical characteristics, family structure, parental attitudes, adaptational processes such as self-esteem, and quality of life so that at-risk children can be identified early and potential interventions can be developed.

CHAPTER 5: COMPARISON OF PARENT- AND CHILD-REPORTED QUALITY OF LIFE AMONG ADOLESCENTS WITH CONGENITAL HEART DISEASE

Introduction

Congenital heart disease (CHD) is the most common type of birth defect affecting almost 1% of births in the United States.[1,2] Advancements in treatment over the last several decades have dramatically improved the survival rate in these patients so that, recently, 85-90% were estimated to reach adulthood.[4,98] Additionally, one study estimated that the median age of patients with CHD increased from 11 years in 1985 to 17 years in 2000 and that this age is likely to continue increasing.[116] This shift in the age of survivors necessitates research on the long term impacts of this condition and its treatments.

Previous studies suggest that children with CHD are more likely to experience cognitive deficits compared with healthy peers including increased prevalence of developmental disabilities, lower social cognition, speech and language difficulties, and poorer executive functioning[28,100] Children with CHD, especially those with more severe forms, may also have real or perceived exercise restrictions that lead to limited involvement in sports, inadequate physical activity, and obesity.[94,117-119] All of these issues could contribute to poorer quality of life (QOL) which is an important outcome to assess because the well-being of these individuals should be optimized in addition to survival. Quality of life considers more than the physical morbidity of a chronic condition by combining it with an individual's perception of psychological and social

functioning.[120] It is also an important outcome because it could help guide intervention services to improve functionality in this group.

Part of the definition of quality of life is that it entails an individual's perception. Many studies of these outcomes rely solely on parent-report of this outcome, but child-report is also important to assess.(ref) Therefore, the purpose of this study is to compare parent- and child-reported quality of life in adolescents with CHD.

Methods

Data were obtained on all children born between 1998 and 2003 surgically treated for CHD at Children's Healthcare of Atlanta (CHOA). CHOA treats almost all cases of CHD in Georgia. Information on surgeries related to CHD treatment, mortality information, and contact information were obtained from CHOA clinical records. We obtained more updated contact information by linking the parent or guardian of each child to current addresses and telephone numbers using Accurint, a commercial company that provides contact information from sources like credit cards, because children may not have been seen recently in CHOA facilities.

Children were excluded if they were known to be deceased (N = 235), had inadequate contact information (N = 117), or their parents could not complete the questionnaires in English (N = 9). We also excluded those with certain syndromes related to the outcomes of interest (N = 289) including 22q 11.2 deletion, Down, Holt-Oram, Loeys-Dietz, Triple X, Trisomy 18, Turner, VACTERL, and William's because the impact of these syndromes on quality of life would likely be greater than any potential impact from the CHD and its treatments.

We attempted to contact all families of the eligible children by mail and then by telephone if the family had not responded within two weeks. Parents were asked to complete a questionnaire about their child with CHD and the child with CHD was also asked to complete a short questionnaire about themselves.

Quality of Life

Both the parent and child questionnaires included the Pediatric Quality of Life Inventory (PedsQL), Version 4.0 which is well-validated instrument designed to measure health-related quality of life at various ages.[129,130] The generic core for children (8 – 12 years old) and teens (13 – 18 years old) includes physical functioning, emotional functioning, social functioning, and school functioning. The cardiac module was also included which asks about quality of life related to areas specific for children with chronic heart conditions such symptoms and treatment. Items on the parent report version are the same as those on the child report form except that parents are asked in reference to "your child" whereas the child is asked about themselves. Each item is ranked by the respondent on a Likert scale from 'never a problem' to 'always a problem'. Responses are then transformed to a scale of 0 to 100, and these scores are averaged across items for each scale. Higher scores indicate better quality of life. The physical health score is equivalent to the physical functioning score, and psychosocial health is the average of items in the emotional, social, and school functioning scales. All four separate scales are averaged for the total score. [129]

Analysis

Mean and median scores were compared between the parent and child on all scales of the generic core and the cardiac module using paired t tests and sign rank tests respectively. Scores reported by the parent and the child were also compared with normative samples. Agreement between parent and child responses was assessed using concordance correlation coefficients (r_c). All analyses were conducted using SAS 9.4.

Results

Of the 497 families in which the parent completed the questionnaire about their child with CHD, 486 completed the PedsQL section. Among these, 420 adolescents with CHD also completed the PedsQL section about themselves. Both the parent and the adolescents reported quality of life below the normative populations in all scales in the generic core except emotional functioning. Parents and children reported similar median scores in all of these scales except emotional functioning. In this scale the adolescents reported lower quality of life than the parents, 80.0 vs. 90.0. The concordance correlation coefficients indicated moderate agreement between parent and child response in all scales, but slightly lower agreement in emotional (r_c = 0.57) and social functioning (r_c = 0.56) (Table 5.1). On the cardiac module, median parent- and child-reported scores only differed in symptoms for which the adolescents reported lower quality of life (child-report = 78.6, parent-report = 85.7). Agreement was also moderate on the cardiac module scales ranging from 0.48 in communication to 0.68 in symptoms (Table 5.2).

Table 5.1. Parent- and child-reported quality of life for adolescents with CHD on the generic core scales of the PedsQL

		Parent Report		Child report			
		Normative sample	**CHD N = 420**	***Normative sample***	**CHD N = 420**	**p-value[1]**	r_c
Total	**Mean (SD)**	*81.3 (15.9)*	78.7 (17.5)*	*82.9 (13.2)*	78.4 (17.1)*	0.60	0.67
	Median (IQR)		82.6 (66.3, 92.9)		81.5 (69.6, 92.4)	0.21	
Physical health	**Mean (SD)**	*83.3 (20.0)*	80.6 (21.0)*	*86.9 (13.9)*	80.6 (19.1)*	0.99	0.62
	Median (IQR)		87.5 (68.8, 100)		84.4 (68.8, 96.9)	0.83	
Psychosocial health	**Mean (SD)**	*80.2 (15.8)*	77.7 (18.1)*	*80.7 (14.7)*	77.1 (18.1)*	0.40	0.64
	Median (IQR)		81.7 (65.0, 93.3)		81.7 (90.0, 65.0)	0.26	
Emotional functioning	**Mean (SD)**	*80.3 (17.0)*	81.5 (20.4)	*78.2 (18.6)*	77.4 (21.9)	<0.01	0.57
	Median (IQR)		90.0 (70.0, 100)		80.0 (60.0, 100.0)	<0.01	
Social functioning	**Mean (SD)**	*82.2 (20.1)*	80.0 (21.8)*	*84.0 (17.4)*	82.5 (18.9)	0.01	0.56
	Median (IQR)		86.3 (65.0, 100)		85.0 (75.0, 100.0)	0.25	
School functioning	**Mean (SD)**	*76.9 (20.2)*	71.8 (21.9)*	*79.9 (16.9)*	71.6 (21.7)*	0.86	0.62
	Median (IQR)		75.0 (55.0, 90.0)		75.0 (60.0, 90.0)	0.16	

*Means significantly different between CHD sample and normative sample using one sample t tests

[1]Means (t tests) and medians (sign rank test) compared between parent- and child-reported scores among CHD group

Table 5.2. Parent- and child-reported quality of life for adolescents with CHD on the cardiac module scales of the PedsQL.

		Parent-report	Child-report	p-value[1]	r_c
Symptoms	**Mean (SD)**	81.4 (19.4)	76.1 (19.7)	<0.01	0.68
	Median (IQR)	85.7 (71.4, 96.4)	78.6 (64.3, 92.9)	<0.01	
	Missing	1	2	3	
Physical appearance	**Mean (SD)**	78.8 (24.5)	75.8 (28.1)	0.01	0.62
	Median (IQR)	83.3 (66.7, 100)	83.3 (58.3, 100)	0.14	
	Missing	4	3	7	
Treatment anxiety	**Mean (SD)**	78.0 (28.2)	78.1 (26.5)	0.92	0.59
	Median (IQR)	87.5 (62.5, 100)	87.5 (62.5, 100)	0.76	
	Missing	5	3	8	
Cognitive problems	**Mean (SD)**	68.9 (26.3)	68.7 (25.0)	0.86	0.65
	Median (IQR)	70.0 (50.0, 95.0)	70.0 (50.0, 90.0)	0.27	
	Missing	5	2	7	
Communication	**Mean (SD)**	76.5 (27.7)	75.6 (27.3)	0.51	0.48
	Median (IQR)	83.3 (58.3, 100)	83.3 (58.3, 100)	0.22	
	Missing	5	3	8	

[1]Comparison of parent- and child-reported scores using paired t tests (means) and sign rank tests (medians)

Discussion

The results of this study found that parent- and adolescent-report of quality of life agreed moderately well. Agreement between responders was lowest in emotional functioning, social functioning, and communication. This was expected because these and similar areas that involve more internal processes have previously been found to have the lowest agreement in both healthy children and those with a chronic condition.[151] Average scores were similar between parents and children except in a few key areas including emotional functioning and symptoms in which the adolescent with CHD reported lower quality of life than their parent.

A study of quality of life in healthy children 5 to 8 years old which also the PedsQL found much lower agreement between parent and child report than we found in our study. The intra-class correlations for this previous study were no higher than 0.23 in any area.[152] Additionally, other research has suggested that on average children with CHD typically report better quality of life than their parents.[83,125] However, at least one study found that quality of life was only lower than the normative sample in the child self-report and not the parent-report.[122] We did not quite see either of these relationships, but studies in other populations have noted more agreement between patient- and parent-report in older children. This convergence may occur because as children age they learn more about their heart condition and they are better able to communicate their needs with parents.[153,154] Therefore, we may not see much of a difference because we only included older ages.

A strength of this study is that we assessed agreement in parent- and child-report using the concordance correlation coefficient. Much of previous research that included

parent and child report often only assessed average differences. However, as we found, these different statistical methods can give somewhat different results. Additionally, the concordance correlation coefficient was chosen because it only provides large correlations if the absolute difference between values for each pair are small. However, it can give falsely high correlations if there is more variation in the sample.[155] Therefore, we also calculated Pearson correlation coefficients (not shown) which were very similar.

One limitation of this study is that we had to exclude families from which the child did not return a questionnaire. Approximately a third of these were reported by the parent to be mentally or physically unable to complete the child questionnaire. For these families, agreement is irrelevant because proxy-report must be used. In the other cases of child non-response, if these adolescents are different from those who participated this may cause selection bias. However, we did not observe meaningful differences in clinical and demographic characteristics between these groups. These differences would also have to be related to agreement to cause bias. From previous studies, the other factor which has been found to be related to agreement is parent quality of life, but it is unclear how this would affect whether the child responded.[152]

In conclusion, the findings of this study suggest that parent-report may be a useful and reliable proxy for older children with CHD, but obtaining self-report from the adolescent is still ideal when possible. Future research should utilize agreement statistics when parent and child reports are included and should assess other factors related to agreement in populations with chronic conditions.

CHAPTER 6. CONCLUSION AND FUTURE DIRECTIONS

Conclusions

Improved treatment and diagnosis of CHD has greatly reduced the mortality of affected individuals.[4,98] Therefore, as children affected with CHD live longer it has become imperative to understand other challenges these patients may face. Research has shown that children with CHD are at an increased risk for cognitive and other developmental differences, but the relationship between CHD and other adverse outcomes has been less clear, especially in adolescence for which research is less abundant.[28,100] Available studies are also limited by small convenience samples, lack of information to address potential confounding in comparison groups, and a focus on those with the more severe forms of CHD. This dissertation sought to address these limitations by assessing behavior, quality of life, and self-esteem in a large sample of adolescents surgically treated for a CHD and comparing these outcomes between those affected, siblings without a birth defect, and population norms.

Behavior problems in adolescents with CHD were assessed using parent-report on the Child Behavior Checklist. Parents reported increased internalizing behavior problems, such as anxiety and depression, for their child with CHD compared with their sibling, but there was no difference in externalizing behavior. Seventeen percent of the children with CHD were reported to have clinically significant internalizing behavior problems compared with the expected 10% from population norms for this instrument.[105] This equated to more than two times greater odds of clinically significant behavior problems among children with CHD than their sibling. Parents also reported lower quality of life for their child with CHD compared with their siblings on all composite

scores measured by the PedsQL, physical health, psychosocial health, and total quality of life. After adjusting for gender and age, the child with CHD scored almost half a standard deviation lower on physical and psychosocial health than their unaffected sibling. These differences were smaller but still meaningful between those with the least severe forms of CHD and their siblings.

Adolescents' perspective of the impact of CHD on their daily lives was assessed through self-perception measured using the Harter Self-Perception Profile and self-reported quality of life on the PedsQL. Although the adolescents with CHD generally reported normal self-esteem they reported lower quality of life than normative samples of healthy children. Increased severity of CHD was associated with lower perceived physical health, psychosocial health, and quality of life related to symptoms. However, after adjustment, other factors including household income and total number of cardiac surgeries were more strongly related to quality of life than defect severity.

The results of this dissertation suggest that those with CHD face behavioral and quality of life challenges even years after the defect has been repaired. As these differences were not only observed in those with the most severe forms of CHD, and defect severity does not appear to be the strongest influence on these outcomes, parents and clinicians should monitor all children with CHD requiring surgical intervention.

Strengths

As part of this dissertation Studying the Impact of Congenital Heart Disease (StICHD) was conducted to address the research question of interest by obtaining parent- and self-reported information on teens with CHD. This study is unique in that it also

collected information from the parents on a sibling without a birth defect to use as a comparison group. Previous research has generally only compared affected individuals with normative samples for which information on important confounders, such as socioeconomic status, is not available. Studies that do utilize other comparison groups still are often not able to address all sources of confounding. The advantage of using siblings without a birth defect as a comparison group is that they not only allow for the control of confounders that could be measured, such as socioeconomic status, but also factors that would be harder to quantify such as early life environment, parental stress, and parent expectation.

Another limitation of previous literature is its frequent use of convenience samples recruited from patients currently being seen in cardiac clinics. Reflecting trends of those lost to follow up in cardiac care centers, these samples may be more severely affected and of higher socioeconomic group and therefore would not be generalizable to the entire CHD population.[114] In StICHD our baseline cohort included all children born between 1998-2003 surgically treated for CHD. We think that this cohort should be fairly representative of the CHD population because almost all children with a CHD in the state of Georgia are treated at CHOA. In attempt to maintain this generalizability we did not limit our recruitment to only those who were current patients. In addition, we combined contact information from the medical record with contact information from Lexis Nexus' Accurint in order to obtain more current information for families who had not recently been seen in CHOA facilities.

Clinical information was obtained from the entire baseline cohort and linked with the parent and child response for those who participated in the study. This information

not only provided clinical information relevant to the outcomes of interest, but also allowed us to compare responders and nonresponders. Furthermore, these factors were used to adjust for any differences between response groups using inverse probability of treatment weighting to estimate the potential impact of selection bias and further maintain generalizability.

An important aspect of this dissertation was to assess whether differences between those with CHD and healthy peers were mainly driven by issues in children with the more severe forms of CHD or whether differences could also be observed in children with milder forms. In order to do this, we classified CHD into three severity categories, critical single ventricle, critical two ventricle, and noncritical, which are distinguished by general treatment characteristics and residual cardiovascular changes and restrictions. To classify individuals we used CHD diagnoses and treatment information from the clinical records. This is ideal over using ICD-9 codes or diagnoses alone because the severity of a defect and the sequelae of treatments and cardiovascular insults can vary between children with the same underlying type of defect. Therefore, we hope that our classification method created more homogeneous groups.

All three outcomes of interest in this study were measured using well-validated instruments for which normative samples were available. This provided us with another comparison group, in addition to the unaffected siblings, and allowed for comparison with other studies. Additionally, clinically significant cutpoints have been established for the CBCL, used to measure behavior, and the PedsQL which measures quality of life.[105,129] These provide easier interpretation of the clinically relevant impact of CHD in our population. We were also able to measure quality of life in the adolescents using

parent- and self-report. This is important because part of the definition of quality of life is that it is an individual's perspective,[120] and other studies have shown that parent- and child-report do not always agree.[125] It seems like children may have a more accurate perspective on daily challenges they face socially and academically. However, parents may better understand their child's condition including restrictions they face. Therefore, both perspectives are important to consider. The PedsQL is also a useful tool for measuring quality of life because it contains questions that make up the generic core, which are applicable to healthy children and those with a chronic condition, but also has a cardiac module which includes aspects of quality of life specifically of importance to those with a chronic heart condition. Therefore, the generic core allows for comparison between those with CHD and healthy peers in areas important to all children, but the cardiac module potentially highlights other important areas of concern.

Finally, this study benefits from the extensive amount of information collected from parents in the questionnaires. This information includes additional clinical information, demographic information, comorbidities the child may have, medication use, family structure, and information about time spent after school. This information allowed for a more comprehensive assessment of characteristics associated with quality of life in these adolescents. Specifically, many of these factors, including self-esteem and physical activity, have been shown to account for large amounts of variation in self-reported quality of life, but previous studies had not evaluated all of these factors together. Therefore, for example, we were able to assess the association between physical activity and quality of life independent of the potential effect of self-esteem. We

could also consider the relative effects of participation in sports versus participation in other clubs or organizations and other time spent with friends.

Weaknesses

Despite its strengths, this dissertation had several limitations that should be considered. The primary limitation is the low response rate in the study (32%). This mainly resulted from our inability to locate families despite the use of Accurint contact information. Considering this difficulty, we hypothesized that responders would be more likely to be those more recently seen in CHOA facilities and therefore would be more likely to be higher socioeconomic status and those with more severe CHD or comorbidities who would require closer follow up. Additionally, it may be more difficult to trace families with greater residential mobility, including those with lower socioeconomic status. Although we did see differences related to these characteristics in the bivariate analysis, it is reassuring that our sensitivity analysis using inverse probability of treatment weighting did not suggest meaningful selection bias. Nevertheless, we cannot exclude the possibility that we did not find a difference because we did not have information on certain important covariates, such as socioeconomic status, for the baseline cohort. Also, even if selection bias is present, our sibling comparison should not be impacted because the children with CHD are being compared to their sibling which matches these groups on all shared familial factors. In addition to potential selection bias, the low response rate also reduced the sample size of our study. This reduced our ability to conduct certain analyses in certain subgroups and assess specific defects individually. Nevertheless, our study sample is still larger than many in previous studies.

Utilization of clinical records provided useful information, but this data was somewhat incomplete. For some individuals, information did not seem to be available for all surgeries the child likely experienced. For example, children with critical single ventricle CHD often require a series of three open heart surgeries in a set sequence to restore blood flow to as close to normal as possible. However, in the cardiac surgeries for which information was available, some of these children are missing earlier surgeries in the sequence. Parent-report of the number of cardiac surgeries undergone by the child were also greater in a number of cases compared with the number for which we had records. In many cases, the medical records appeared to be missing earlier or later surgeries. This may be because older records were not available in the electronic system so may not have been captured in our abstraction or that some surgeries were conducted at other hospitals. Nevertheless, to address this discrepancy, we used parent-report of cardiac surgeries in the regression analysis for child-reported quality of life unless the parent did not provide this information in which case we relied on the medical records. Other clinical variables of interest were also not available or were largely incomplete in the medical record including gestational age, age at diagnosis, and the occurrence of seizures.

Although the aim of the sibling analysis was to minimize confounding, generalizability of findings in this group may be limited. Less than half of the respondents had an eligible sibling for which the parent also completed a questionnaire. Additionally, among the group with CHD, the subset who had a sibling had less behavior problems and better quality of life than those that did not lending further evidence to differences between these groups. The sibling comparison may also dampen the true

effect of CHD if having a child with a chronic condition impacts the quality of life of all children in the family. We cannot fully assess this in our study without a healthy nonrelated group, but the siblings in our study had less behavior problems and higher quality of life scores than expected from the normative populations. Some have suggested the presence of a child with a chronic condition can bring a family closer which seems congruent with our findings. However, this higher quality of life in the siblings may simply reflect differences in confounding covariates between our sample and the normative population. Given this and worse outcomes in the CHD group without an affected sibling, differences in outcomes between those with CHD and healthy children may be even greater than the sibling comparison suggests.

Although we can somewhat control for parent perception, we cannot exclude the possibility that at least part of the difference we observed in the sibling comparison is due to parents perceiving their child with CHD to have more behavior problems and lower quality of life because of their health history instead of their actual functionality. The parent may also be more overprotective with their child with CHD which has been negatively associated with child quality of life.[128] Related to this, parents may over report better outcomes in the unaffected sibling because they have not had to experience the difficulties of having a birth defect.

Due to limited resources, we did not ask the siblings for which parents completed a questionnaire to return information about themselves. This precluded any comparison of self-reported information between the adolescents with CHD and their siblings, and forced use to rely on comparison with normative samples for self-esteem and self-reported quality of life. Without information on important covariates in the normative

samples, this comparison is vulnerable to confounding. We tried to minimize this in our comparison of self-esteem by standardizing the normative means by gender and grade level, but we could not adjust for other covariates or use this strategy for quality of life.

Generalizability may also be an issue for the outcomes which relied on response from the child with CHD, self-esteem and quality of life, because in about one fourth of the families for which a parent responded the adolescent did not provide information that could be used in analyses. This group included those who were not able to participate, those who chose not to participate, and those who did not complete the instruments fully or correctly. This may suggest our findings on the child-reported outcomes are more positive than they would be in the full CHD population because those excluded are likely to have difficulties. This is supported by the small increase in comorbidities between adolescents who participated and those whose parent participated but they did not.

In this dissertation we attempted to assess characteristics associated with self-reported quality of life among the adolescents with CHD. However, as this study was cross-sectional, we could not establish temporality of many of these factors and therefore could not interpret the results as causal. Most specifically this was an issue for our assessment of the relationship between self-esteem, quality of life, and participation in sports. All three factors were strongly association, but it is unclear whether self-esteem leads to quality of life or the reverse is true. Additionally, participation in sports may be a cause, mediator, or result of these outcomes. Likely, these and other factors all affect each other over time as the child develops. Although these associations are important we were only able to assess them in an exploratory manor because of this limitation.

Future directions

The findings of this dissertation strengthen the evidence that individuals with CHD are at an increased risk for behavior problems and lower quality of life. However, the determinants of these outcomes are still unclear in the CHD population. As we demonstrated, those with the most severe forms of CHD report the most problems, but this association is not as clear after adjustment for other characteristics. We also found that those with mild forms of CHD who completed treatment years before may still face increased difficulties compared with healthy peers. Future research should attempt to identify determinants of behavior problems and low quality of life in individuals with CHD so that clinicians can better identify at-risk children to monitor, and so that interventions can be explored to improve these outcomes. Likely, part of the lack of clarity in causality of long term outcomes such as behavior and quality of life is due to their multifactorial nature. Characteristics of the family, academic challenges, social interactions, behavior, quality of life, and self-esteem all have complex relationships that can change and affect each other over time. Therefore, future research should collect data longitudinally to observe such changes as the child develops.

Research has previously demonstrated that having a child with CHD can lead to parental stress, and that this in turn may impact psychological outcomes in children with CHD. However, research has not been conducted to assess the potential impact of CHD on a sibling or what impact a healthy sibling may have on the development of a child with CHD. Our research found some evidence of effect modification in the association between CHD and behavior problems by the presence of an older versus younger sibling. Although these findings should be considered exploratory, it raises the question of the role of a healthy sibling in a family with a child with CHD. It could be useful for future

research to examine whether such a sibling helps the child with CHD develop more normally, whether having a brother or sister with a CHD has a negative impact on the development of the healthy sibling, or whether having other unaffected children impacts the parents' perception of the health of their child with CHD.

Finally, as surgical techniques and interventions continue to improve, future research will need to continue to evaluate long term outcomes in the CHD population to assess changing needs in this population. The group that will likely be most impacted by such improvements are those with the most severe forms of CHD. Currently, mortality for patients with critical CHD remains around 30% before the age of 18 compared with 5% in noncritical.[4] This means that if survival continues to improve, likely the population with critical CHDs will continue to grow faster than the rest of the CHD population. This group also experiences high levels of behavior problems, as this dissertation points out, along with other developmental disabilities and cognitive impairments. Therefore, services for children with CHD may need to be increased overtime to ensure they can keep up with increasing demand.

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