Published in final edited form as:

J Pediatr. 2019 January ; 204: 38–45.e1. doi:10.1016/j.jpeds.2018.08.069.

Longitudinal Associations between Neurodevelopment and Psychosocial Health Status in Patients with Repaired D-Transposition of the Great Arteries

Victoria K. Robson, MD, Christian Stopp, MS, David Wypij, PhD, Carolyn Dunbar-Masterson, RN, BSN, David C. Bellinger, PhD, MSc, David R. DeMaso, MD, Leonard A. Rappaport, MD, and Jane W. Newburger, MD, MPH

Departments of Medicine (VKR), Cardiology (CS, DW, CDM, DRD, JWN), Neurology (DCB), Psychiatry (DCB, DRD), and Pediatrics (LAR), Boston Children's Hospital, Boston, MA; the Departments of Pediatrics (VKR, DW, DRD, LAR, JWN), Neurology (DCB), and Psychiatry (DCB, DRD), Harvard Medical School, Boston, MA; and the Department of Biostatistics (DW), Harvard T.H. Chan School of Public Health, Boston, MA.

Abstract

Objective: To examine associations between measurements of neurodevelopment and psychosocial health status at age 8 and 16 years in patients with repaired dextro-transposition of the great arteries (D-TGA).

Study design: In the 16-year follow-up of the Boston Circulatory Arrest Study, 137 parents completed the Child Health Questionnaire – Parent Form-50 (CHQ-PF50), of whom 135 had completed the CHQ-PF50 when their child was age 8 years. Psychosocial and physical summary scores were used to assess change in health status from age 8 to 16 years. A comprehensive battery of neurodevelopmental testing was performed at ages 8 and 16 to examine associations with adolescent health status.

Results: Lower psychosocial summary scores of D-TGA subjects at 16 years were highly associated with numerous concurrent domains of neurodevelopmental function, most notably with higher (worse) scores on the Conners' ADHD/DSM-IV Scales (parent: $r = -0.62$, $P < 0.001$; adolescent: $r = -0.43$, $P < .001$) and the Behavior Rating Inventory of Executive Function Global Executive Composite (parent: $r = -0.66$, $P < 0.001$; adolescent: $r = -0.39$, $P < 0.001$). Psychosocial and physical summary scores tracked from ages 8 to 16 years ($r = 0.44$ and 0.47 , respectively, $P < 0.001$ for each). Higher (worse) scores of multiple attention measures at age 8 years predicted worse psychosocial summary scores at 16 years.

Corresponding author: Jane W. Newburger, MD, MPH, 300 Longwood Avenue, Boston Children's Hospital, Department of Cardiology, Boston, MA 02115, Telephone: 617-355-5427, Fax: 617-739-3784, Jane.Newburger@cardio.chboston.org.

Portions of this study were presented at the Annual Scientific Session of the American Heart Association, November 8–12, 2008, New Orleans, Louisiana.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions: Attention deficits at age 8 were highly predictive of worse psychosocial health in adolescence. Further studies are needed to assess whether treatment of childhood ADHD (attention deficit hyperactivity disorder) could improve adolescent well-being.

Keywords

congenital heart disease; pediatrics; transposition of great vessels; quality of life; surgery; brain; adolescents

Survival for children with critical congenital heart disease (CHD) has improved with innovations in cardiac surgical and medical management over the past three decades, but with a high prevalence of neurodevelopmental deficits in this population.^{1,2} The adolescent years are a time when such neurodevelopmental impairment may be expected to especially impact a child's health-related quality of life (HRQoL).³⁻⁵ The psychosocial health status of adolescents with CHD has become an important issue, with CHD guidelines and parent advocacy groups emphasizing psychosocial in addition to medical needs.⁶⁻⁸

Individuals with dextro-transposition of the great arteries (D-TGA) are one of the best-studied CHD populations. D-TGA is the second most common critical congenital heart defect, causing diminished cerebral oxygen delivery both in fetal life and at birth.^{9, 10} Surgical correction via the arterial switch operation (ASO) is now performed in the neonatal period,¹¹ with high event-free survival.^{12, 13} We have previously reported on health status at 8 years of age as measured by the Child Health Questionnaire (CHQ) in a cohort of patients with D-TGA who were enrolled in early infancy in the Boston Circulatory Arrest Study (BCAS). This work demonstrated that neurodevelopmental performance (intelligence, academic achievement) is impaired and associated with worse concurrent psychosocial health status in children with repaired D-TGA.¹⁴

Understanding the determinants of HRQoL, or health status,¹⁵ in adolescents after infant congenital heart surgery is essential to providing life-long care to this patient population. Very few studies to date have examined factors associated with longitudinal psychosocial and physical health status in adolescents with CHD. McCrindle et al demonstrated that development of clinical comorbidities predicted deterioration in functional physical health status in adolescents after the Fontan procedure.¹⁶ In addition to presenting the association between concurrent neurodevelopmental impairment and health status at 16 years, we evaluated whether neurodevelopmental deficits at 8 years were predictive of subsequent psychosocial health status at 16 years.

Methods

The study methods of the BCAS and neurodevelopmental findings of its participants from the perioperative period through age 16 years have previously been described.¹⁷⁻²¹ In brief, patients with D-TGA were assigned to a support method consisting of either predominantly deep hypothermic circulatory arrest (DHCA) or predominantly low-flow cardiopulmonary bypass during the ASO. Criteria for enrollment in the BCAS included diagnosis of D-TGA with intact ventricular septum or ventricular septal defect, ASO by age three months, birth weight $\geq$ 2.5 kg, no recognizable syndrome or extra-cardiac anomalies of greater than minor

severity, no previous cardiac surgery, and no anomaly requiring aortic arch reconstruction or additional open-surgical procedures. D-TGA subjects in the current study were enrolled in the BCAS in early infancy and had an in-person evaluation at 16 years (range 13 – 17 years). Subjects living outside the country were excluded.

In addition to a published CHQ normative sample from the general population,²² a referent group of healthy adolescents aged 13 – 17 years was recruited locally. We excluded referent subjects with any form of CHD requiring surgical correction, lack of reading fluency in English by primary caregiver, and criteria employed in the National Institutes of Health (NIH)-funded project, “The NIH MRI study of normal brain development,” which includes any condition that affects the well-being of the brain or indicates suboptimal brain functioning or learning disorder.²³

This protocol was approved by the Institutional Review Board. Informed consent was obtained from parents and guardians, and assent was obtained from all subjects.

The Child Health Questionnaire – Parent Form-50 (CHQ-PF50) was used to assess health status when subjects were approximately 16 years old, and previously when subjects were 8 years old. This 50-item parental questionnaire is a validated and comprehensive multidimensional assessment tool. It is designed to measure health status in children and adolescents and provides summary scores on two dimensions, psychosocial and physical, as well as several subscales. The questionnaire is generic, allowing for comparison of health status among healthy children and children with various medical conditions.²²

Subjects underwent an in-person neurodevelopmental evaluation at both 8 and 16 years using a comprehensive battery of standardized tests. Domains assessed at age 16 years included achievement (Wechsler Individual Achievement Test, Second Edition, WIAT-II²⁴), memory (Children’s Memory Scale, CMS²⁵), visual-perceptual skills (Test of Visual-Perceptual Skills – Revised, TVPS-R²⁶), attention (Conners’ ADHD/Diagnostic and Statistical Manual [DSM]-IV Scales – Parent and Adolescent, CADS-P and CADS-A²⁷), executive function (Behavior Rating Inventory of Executive Function – Parent and Self-Report, BRIEF²⁸ and BRIEF-SR²⁹), and social intelligence (Reading the Mind in the Eyes Test;³⁰ Autism Spectrum Quotient³¹). Domains previously assessed at age 8 years included intelligence (Wechsler Intelligence Scale for Children, Third Edition, WISC-III³²), achievement (WIAT-II²⁴), verbal fluency (Verbal Fluency Task of the McCarthy Scales³³), attention (Conners’ Parent and Teacher Rating Scales, CPRS³⁴ and CTRS;³⁵ Child Behavior Checklist, CBCL;³⁶ Teacher Report Form, TRF;³⁷ Tests of Variables of Attention, ToVA³⁸), and executive function (Wisconsin Card Sort Test;³⁹ Trail-Making Test⁴⁰).

Statistical Analyses:

The primary outcome was the psychosocial summary (PsS) score of the CHQ-PF50. Comparisons of patients with D-TGA to the referent group on demographic measures were made using Fisher exact tests for categorical variables and two-sample *t*-tests for continuous measures. D-TGA patients’ 16-year PsS and physical summary (PhS) scores and their subscale scores were compared with a referent sample using linear regression adjusting for age at CHQ assessment, sex, and concurrent family social class and to the 13 – 15-year CHQ

normative sample using two-sample *t*-tests. Family social class was measured by the Hollingshead Four Factor Index of Social Status.⁴¹ Associations of health status scores at age 16 years with demographic and medical variables were examined using linear regression adjusting for concurrent social class.

A central focus of our study was to characterize associations between 16-year health status scores, particularly PsS scores, with neurodevelopmental testing performed at both age 8 and 16 years. Partial Pearson correlation coefficients adjusting for concurrent social class were used to examine associations of neurodevelopmental measures at age 16 years with concurrent health status. Partial Pearson correlation coefficients adjusting for social class at age 8 years were used to examine associations of neurodevelopmental measures at age 8 years with health status at both age 8 years and age 16 years. The associations between PsS and PhS scores at age 8 compared with 16 years were examined using both paired-sample *t*-tests and Pearson correlation coefficients. Box plots were constructed to examine the distribution of 16-year PsS and PhS scores based on 8-year score tertile. Trends in 16-year scores across 8-year tertiles were assessed using the Jonckheere-Terpstra trend test, with equality of variances assessed using the Levene homogeneity of variability test.

Results

Of 171 subjects with D-TGA enrolled in infancy in the BCAS cohort, 6 died before age 16 and 6 lived out of the country and were excluded from the 16-year evaluation. Of the remaining 159 subjects, 16 (10%) declined to participate and 4 (3%) could not be located. The remaining 139 subjects (87%) were enrolled and completed the neurodevelopmental testing. Of these, 137 parents completed the CHQ-PF50 when their child was 16 years of age, of whom 135 parents had also completed the CHQ-PF50 when their child was 8 years of age. The referent group consisted of 87 local healthy adolescents, of whom the parents of 85 completed the CHQ-PF50.

D-TGA subjects were 16.1 ± 0.5 (mean $\pm$ standard deviation) years of age at CHQ assessment. Most were non-Hispanic Caucasian (91%). They weighed 3.6 ± 0.4 kg at birth, were 39.8 ± 1.3 weeks in gestational age, and had their first operation at 9.9 ± 11.8 days of age. Since the 8-year assessment, 7% (9/137) had any cardiac surgery and 18% (24/137) had any cardiac catheterization. Meanwhile, 4% (6/137) had any cardiac catheterization complication. Other demographic information on this cohort has been previously reported.²¹ The referent subjects were slightly younger (15.2 ± 1.1 years, $P < 0.001$), less likely to be male (55% vs. 77%, $P = 0.001$), and of a higher social class (53.5 ± 9.2 vs. 45.9 ± 12.2 , $P < 0.001$) than the D-TGA subjects, though the groups did not differ in race, weight at birth or gestational age.

Compared with local referents, parents of participants with D-TGA rated their 16-year-old children as having worse overall psychosocial and physical health ($P < 0.001$ and $P = 0.01$, respectively) after adjusting for age, sex, and concurrent social class (Table I). Scores were significantly worse, compared with those of the local referent group, on subscale measures of emotional well-being, behavioral problems, general health, and parental impact. In contrast, parent reports on D-TGA subjects did not differ significantly from those of the

CHQ normative sample in their assessment of overall psychosocial or physical health status as reflected by PsS and PhS scores at age 16 years (Table I). However, the subjects with D-TGA were scored significantly higher than the normative sample on subscales measuring physical limitations/pain, behavioral problems, and parental impact.

Within the D-TGA group, health status summary scores at 16 years, adjusting for concurrent social class, were associated with few demographic and medical variables in linear regression analyses. Lower 16-year PsS scores were associated with older age at ASO ($\beta = -0.13 \pm 0.06$, $P=0.04$), any cardiac surgery since the 8-year assessment ($\beta = -7.6 \pm 2.9$, $P=0.009$), and any cardiac catheterization since the 8-year assessment ($\beta = -4.5 \pm 1.9$, $P=0.02$). Lower 16-year PhS scores were associated with being non-white ($\beta = -4.2 \pm 1.9$, $P=0.03$), older age at ASO ($\beta = -0.10 \pm 0.05$, $P=0.03$), and any cardiac catheterization complication ($\beta = -5.5 \pm 2.7$, $P=0.04$). Neither summary score was associated with other medical history variables such as birth weight; gestational age; Apgar at 1 minute; treatment group assignment; duration of DHCA, cardiopulmonary bypass, or total support times at first operation; duration of intensive care unit or hospital stay at first operation; or seizures.

Relationships in the D-TGA cohort of PsS and PhS scores at age 16 years with concurrent measures of neurodevelopmental function were also examined (Table II). Lower PsS scores were highly associated with higher (worse) CADS-P and CADS-A ADHD Index T scores (CADS-P: $r = -0.62$, $P<0.001$; CADS-A: $r = -0.43$, $P<0.001$) and BRIEF Global Executive Composite scores (parent: $r = -0.66$, $P<0.001$; self-report: $r = -0.39$, $P<0.001$). Lower PsS scores were associated with worse concurrent scores on math achievement, listening comprehension, memory, visual closure (ie, matching of an incomplete target image to the correctly completed image), and social intelligence, and lower PhS scores were associated with lower concurrent scores on math achievement, listening comprehension, memory, and visual closure.

Within the D-TGA cohort, summary measures of psychosocial and physical health did not differ significantly between ages 8 and 16 (Table I). At 16 years as compared with 8 years, scores were significantly higher on the emotional well-being and behavioral problems subscales, though lower on the self-esteem subscale. PsS and PhS scores at age 8 and 16 years were positively associated ($r=0.44$ and $r=0.47$, respectively; $P<0.001$ for each, Figure A and B). There was a significant trend toward higher 16-year scores when moving from the lowest to highest 8-year score tertile ($P<0.001$ for both PsS and PhS). For PsS score, there was substantial variability in 16-year score amongst the lowest tertile of 8-year scorers (Figure C). Significant differences in variability of the 16-year score across the 8-year tertiles were observed (PsS: $P<0.001$, PhS: $P=0.03$).

Among associations between neurodevelopmental function at 8 years and health status at 16 years, higher (worse) scores on measures of attention at 8 years were associated with lower PsS scores at 16 years (Table III). Most notably, lower PsS scores were associated with higher (worse) CPRS Restless-Disorganized and Hyperactive-Immature T scores ($r = -0.39$, $P<0.001$ and $r = -0.41$, $P<0.001$, respectively) and CBCL and TRF Attention Problems T scores ($r = -0.41$, $P<0.001$ and $r = -0.30$, $P<0.001$, respectively). Lower scores on intelligence measures at 8 years were also associated with lower PsS scores at 16 years.

Among the measures of neurodevelopmental function collected at age 8 years, only higher (worse) CBCL Attention Problems T scores were associated with lower PhS scores at age 16 years ($r = -0.26$, $P = 0.003$).

Although some associations between neurodevelopmental function and concurrent PsS and PhS at 8 years in this cohort have been reported previously,¹⁴ they are expanded upon for reference in Table IV (available at www.jpeds.com).

Discussion

Our data suggest that at age 16 years, adolescents with repaired D-TGA have parent-reported psychosocial and physical health status that is worse than that of a local referent group of healthy adolescents, but similar to that of the CHQ normative sample. Building upon our previous work demonstrating associations between neurodevelopmental status and psychosocial health in elementary school children with D-TGA,¹⁴ we demonstrated that significant associations persist between concurrent neurodevelopmental outcomes and psychosocial health at age 16, particularly with regard to attention and executive function. PsS scores between elementary school (age 8) and high school (age 16) were significantly correlated; however, the children in the lowest tertile of PsS scores at age 8 years showed the greatest variability in 16-year scores. Neurodevelopmental impairments at age 8 predicted subsequent psychosocial health at age 16, with deficits in attention being the strongest predictors of future lower psychosocial health status. The associations of attention and executive function with concurrent psychosocial health status have previously been described in children with social stressors and non-cardiac medical illnesses,^{49–52} as well as in children with CHD, including tetralogy of Fallot⁵³ and single ventricle patients who underwent Fontan procedures.¹⁵

Our finding that deficits in attention in elementary school strongly predict worse psychosocial health status in adolescents with CHD has the potential to positively impact the long-term care of these patients. ADHD is reported to be 3 to 4 times more common in patients with CHD compared with the general population,⁵⁴ with a prevalence of 19% in patients with D-TGA by adolescence in our cohort.^{21, 55} Our findings support prior work demonstrating that clinical severity of ADHD is negatively correlated with psychosocial health status, regardless of underlying medical condition.⁵⁶ In the general population, childhood ADHD can increase the risk of several adverse outcomes in adolescence, including graduation failure and juvenile justice system involvement.⁵⁷ Neurodevelopmental impairment and subsequent poor psychosocial health in adolescents with CHD may portend lower socioeconomic well-being in adulthood.^{58–62} Importantly, our findings have potential implications for clinical care. Pharmacological treatment of ADHD has been shown to improve psychosocial HRQoL over time⁶³ and its use is considered safe in children with CHD.⁶⁴ However, further research is needed to evaluate whether identification and treatment of ADHD in elementary age children with CHD can improve their psychosocial well-being into adulthood.

The findings of this study should be interpreted in light of several limitations. We are unable to determine causality in the relationship between neurodevelopmental status and

psychosocial health. Similarly, our study design did not allow us to reach an inference about whether treatment of ADHD in the interim between ages 8 and 16 years improved HRQoL. In addition, older age at ASO was associated with lower 16-year PsS and PhS scores; older age has been colinear with diagnosis of VSD and worse neurodevelopmental outcomes in our cohort, limiting causal inference.^{18–21} The CHQ is a generic instrument, rather than a cardiac-specific tool such as the Pediatric Cardiac Quality of Life Inventory⁶⁵ or Pediatric Quality of Life Inventory.⁶⁶ Moreover, this study used a subjective questionnaire, with answers provided by parents as a proxy for assessment of quality of life in adolescents. We chose to use the parental questionnaire because there are no summary scores or published US normative sample for the Child Health Questionnaire – Child Form-87 report.²² Although it is possible that health perceptions of children may differ from those of parents, moderate to strong correlations have been demonstrated between adolescent self-report and parent-proxy report of HRQoL, though the strength of association diminishes as patients grow older.⁶⁷ Our findings are consistent with other studies reporting superior or equivalent HRQoL in D-TGA patients compared with published normative control groups,⁶⁹ but impaired HRQoL compared with locally recruited healthy referents.¹³ Lower educational and socioeconomic status in the general US population, as well as inclusion of children with neurodevelopmental disabilities, may have resulted in lower parent rating of child HRQoL in the CHQ normative sample.⁷⁰ In addition to a normative sample, we chose to use local healthy referents, who had neurodevelopmental outcomes and general health status superior to that of D-TGA subjects. The local reference sample provides an optimal regionally-matched benchmark to aim for in the care of adolescents with D-TGA and other congenital heart defects.

This study provides further evidence to support efforts to identify and treat ADHD in children with D-TGA and other forms of CHD in order to improve their long-term psychological well-being.

Acknowledgments

Supported by the National Heart, Lung, and Blood Institute (R01 HL77681 [to J.N.]) and the Farb Family Fund (to J.N.). The authors declare no conflicts of interest.

Glossary of Abbreviations

ADHD	Attention deficit hyperactivity disorder
ASO	Arterial switch operation
BCAS	Boston Circulatory Arrest Study
BRIEF	Behavior Rating Inventory of Executive Function – Parent
BRIEF-SR	Behavior Rating Inventory of Executive Function – Self-Report
CADS-A	Conners' ADHD/DSM-IV Scales – Adolescent
CADS-P	Conners' ADHD/DSM-IV Scales – Parent
CBCL	Child Behavior Checklist

CHD	Congenital heart disease
CHQ-PF50	Child Health Questionnaire – Parent Form-50
CMS	Children’s Memory Scale
CPRS	Conners’ Parent Rating Scales
CTRS	Conners’ Teacher Rating Scales
DHCA	Deep hypothermic circulatory arrest
D-TGA	Dextro-transposition of the great arteries
HRQoL	Health-related quality of life
ToVA	Tests of Variables of Attention
TRF	Teacher Report Form
TVPS-R	Test of Visual-Perceptual Skills – Revised
WIAT-II	Wechsler Individual Achievement Test, Second Edition
WISC-III	Wechsler Intelligence Scale for Children, Third Edition

References

- [1]. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation*. 2010;122:2264–72. [PubMed: 21098444]
- [2]. Marelli A, Miller SP, Marino BS, Jefferson AL, Newburger JW. Brain in congenital heart disease across the lifespan: the cumulative burden of injury. *Circulation*. 2016;133:1951–62. [PubMed: 27185022]
- [3]. Kahr PC, Radke RM, Orwat S, Baumgartner H, Diller GP. Analysis of associations between congenital heart defect complexity and health-related quality of life using a meta-analytic strategy. *Int J Cardiol*. 2015;199:197–203. [PubMed: 26204568]
- [4]. Latal B, Helfricht S, Fischer JE, Bauersfeld U, Landolt MA. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: a systematic review. *BMC Pediatr*. 2009;9:6. [PubMed: 19161602]
- [5]. Drakouli M, Petsios K, Giannakopoulou M, Patiraki E, Voutoufianaki I, Matziou V. Determinants of quality of life in children and adolescents with CHD: a systematic review. *Cardiol Young*. 2015;25:1027–36. [PubMed: 25683247]
- [6]. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *Circulation*. 2008;118:2395–451. [PubMed: 18997168]
- [7]. Connelly MS, Webb GD, Somerville J, Warnes CA, Perloff JK, Liberthson RR, et al. Canadian consensus conference on adult congenital heart disease 1996. *Can J Cardiol*. 1998;14:395–452. [PubMed: 9551034]
- [8]. Report of the British Cardiac Society Working Party. Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK. *Heart*. 2002;88 Suppl 1:i1–14. [PubMed: 12181200]

- [9]. Martins P, Castela E. Transposition of the great arteries. *Orphanet J Rare Dis.* 2008;3:27. [PubMed: 18851735]
- [10]. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation.* 2015;131:1313–23. [PubMed: 25762062]
- [11]. Villafane J, Lantin-Hermoso MR, Bhatt AB, Tweddell JS, Geva T, Nathan M, et al. Dtransposition of the great arteries: the current era of the arterial switch operation. *J Am Coll Cardiol.* 2014;64:498–511. [PubMed: 25082585]
- [12]. Haas F, Wottke M, Poppert H, Meisner H. Long-term survival and functional follow-up in patients after the arterial switch operation. *Ann Thorac Surg.* 1999;68:1692–7. [PubMed: 10585044]
- [13]. de Koning WB, van Osch-Gevers M, Ten Harkel AD, van Domburg RT, Spijkerboer AW, Utens EM, et al. Follow-up outcomes 10 years after arterial switch operation for transposition of the great arteries: comparison of cardiological health status and health-related quality of life to those of the a normal reference population. *Eur J Pediatr.* 2008;167:995–1004. [PubMed: 17987315]
- [14]. Dunbar-Masterson C, Wypij D, Bellinger DC, Rappaport LA, Baker AL, Jonas RA, et al. General health status of children with D-transposition of the great arteries after the arterial switch operation. *Circulation.* 2001;104:1138–42. [PubMed: 11568045]
- [15]. McCrindle BW, Williams RV, Mitchell PD, Hsu DT, Paridon SM, Atz AM, et al. Relationship of patient and medical characteristics to health status in children and adolescents after the Fontan procedure. *Circulation.* 2006;113:1123–9. [PubMed: 16490823]
- [16]. McCrindle BW, Zak V, Breitbart RE, Mahony L, Shrader P, Lai WW, et al. The relationship of patient medical and laboratory characteristics to changes in functional health status in children and adolescents after the Fontan procedure. *Pediatr Cardiol.* 2014;35:632–40. [PubMed: 24264999]
- [17]. Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban KC, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus lowflow cardiopulmonary bypass in infant heart surgery. *N Engl J Med.* 1993;329:1057–64. [PubMed: 8371727]
- [18]. Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N Engl J Med.* 1995;332:549–55. [PubMed: 7838188]
- [19]. Bellinger DC, Wypij D, Kuban KC, Rappaport LA, Hickey PR, Wernovsky G, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation.* 1999;100:526–32. [PubMed: 10430767]
- [20]. Bellinger DC, Wypij D, duPlessis AJ, Rappaport LA, Jonas RA, Wernovsky G, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg.* 2003;126:1385–96. [PubMed: 14666010]
- [21]. Bellinger DC, Wypij D, Rivkin MJ, DeMaso DR, Robertson RL, Jr., Dunbar-Masterson C, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation.* 2011;124:1361–9. [PubMed: 21875911]
- [22]. Landgraf JM, Abetz L, Ware JE. The Child Health Questionnaire (CHQ): A user's manual. Boston (MA): The Health Institute, New England Medical Center; 1996.
- [23]. Evans AC, Brain Development Cooperative Group. The NIH MRI study of normal brain development. *Neuroimage.* 2006;30:184–202. [PubMed: 16376577]
- [24]. Wechsler D Wechsler Individual Achievement Test 2nd Edition (WIAT II). London: Psychological Corp; 2005.
- [25]. Cohen M Children's Memory Scale. San Antonio (TX): Psychological Corp; 1997.
- [26]. Gardner MF. TVPS(UL)-R. Test of Visual-Perceptual Skills (non-motor) (Upper Level) Revised. Hydesville (CA): Psychological and Educational Publications, Inc; 1997.

- [27]. Conners CK. Conners' Rating Scales-Revised. North Tonawanda (NY): Multi-Health Systems Inc; 1997.
- [28]. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior Rating Inventory of Executive Function. Odessa (FL): Psychological Assessment Resources; 2000.
- [29]. Guy SC, Isquith PK, Gioia GA. Behavior Rating Inventory of Executive Function-Self-Report Version. Odesa (FL): Psychological Assessment Resources; 2004.
- [30]. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psych*. 2001;42:241–51.
- [31]. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord*. 2001;31:5–17. [PubMed: 11439754]
- [32]. Wechsler D Wechsler intelligence scale for children-third edition. San Antonio (TX): Psychological Corporation; 1991.
- [33]. McCarthy D The McCarthy scales of children's abilities. New York (NY): Psychological Corporation; 1972.
- [34]. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;26:257–68. [PubMed: 9700518]
- [35]. Conners CK, Sitarenios G, Parker JD, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;26:279–91. [PubMed: 9700520]
- [36]. Achenbach TM. Manual for the child behavior checklist/4–18 and 1991 profile. Burlington (VT): Dept. of Psychiatry, University of Vermont; 1991.
- [37]. Achenbach TM. Manual for the teacher's report form and 1991 profile. Burlington (VT): University of Vermont; 1991.
- [38]. Greenberg LM, Waldman ID. Developmental normative data on the test of variables of attention (T.O.V.A.). *J Child Psychol Psychiatry*. 1993;34:1019–30. [PubMed: 8408366]
- [39]. Heaton RK, Psychological Assessment Resources Inc. Wisconsin Card Sorting Test manual Revised and expanded. ed Odessa (FL): Psychological Assessment Resources; 1993.
- [40]. Reitan RM, Davison LA. Clinical neuropsychology: current status and applications. Washington, D.C: Hemisphere Pub. Corp.; distributed by Halsted Press Division, Wiley (NY); 1974.
- [41]. Hollingshead A Four Factor Index of Social Status. New Haven (CT): Yale University, Department of Sociology; 1975.
- [42]. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–72. [PubMed: 17210844]
- [43]. Unolt M, Putotto C, Silvestri LM, Marino D, Scarabotti A, Valerio M, et al. Transposition of great arteries: new insights into the pathogenesis. *Front Pediatr*. 2013;1:11. [PubMed: 24400257]
- [44]. Rivkin MJ, Watson CG, Scoppettuolo LA, Wypij D, Vajapeyam S, Bellinger DC, et al. Adolescents with D-transposition of the great arteries repaired in early infancy demonstrate reduced white matter microstructure associated with clinical risk factors. *J Thorac Cardiovasc Surg*. 2013;146:543–9 e1. [PubMed: 23375991]
- [45]. Rollins CK, Watson CG, Asaro LA, Wypij D, Vajapeyam S, Bellinger DC, et al. White matter microstructure and cognition in adolescents with congenital heart disease. *J Pediatr*. 2014;165:936–44 e1–2. [PubMed: 25217200]
- [46]. Panigrahy A, Schmithorst VJ, Wisnowski JL, Watson CG, Bellinger DC, Newburger JW, et al. Relationship of white matter network topology and cognitive outcome in adolescents with d-transposition of the great arteries. *Neuroimage Clin*. 2015;7:438–48. [PubMed: 25685710]
- [47]. Watson CG, Asaro LA, Wypij D, Robertson RL, Jr., Newburger JW, Rivkin MJ. Altered gray matter in adolescents with d-transposition of the great arteries. *J Pediatr*. 2016;169:36–43 e1. [PubMed: 26553098]

- [48]. Schmithorst VJ, Panigrahy A, Gaynor JW, Watson CG, Lee V, Bellinger DC, et al. Organizational topology of brain and its relationship to ADHD in adolescents with d-transposition of the great arteries. *Brain Behav.* 2016;6:e00504. [PubMed: 27547505]
- [49]. Hrabok M, Sherman EM, Bello-Espinosa L, Hader W. Memory and health-related quality of life in severe pediatric epilepsy. *Pediatrics.* 2013;131:e525–32. [PubMed: 23319535]
- [50]. Sherman EM, Slick DJ, Eyrl KL. Executive dysfunction is a significant predictor of poor quality of life in children with epilepsy. *Epilepsia.* 2006;47:1936–42. [PubMed: 17116035]
- [51]. Laffond C, Dellatolas G, Alapetite C, Puget S, Grill J, Habrand JL, et al. Quality-of-life, mood and executive functioning after childhood craniopharyngioma treated with surgery and proton beam therapy. *Brain Inj.* 2012;26:270–81. [PubMed: 22372414]
- [52]. Allen TM, Anderson LM, Rothman JA, Bonner MJ. Executive functioning and healthrelated quality of life in pediatric sickle cell disease. *Child Neuropsychol.* 2017;8:889–906.
- [53]. Neal AE, Stopp C, Wypij D, Bellinger DC, Dunbar-Masterson C, DeMaso DR, et al. Predictors of health-related quality of life in adolescents with tetralogy of Fallot. *J Pediatr.* 2015;166:132–8. [PubMed: 25444004]
- [54]. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics.* 2008;121:e759–67. [PubMed: 18381503]
- [55]. DeMaso DR, Labella M, Taylor GA, Forbes PW, Stopp C, Bellinger DC, et al. Psychiatric disorders and function in adolescents with d-transposition of the great arteries. *J Pediatr.* 2014;165:760–6. [PubMed: 25063716]
- [56]. Matza LS, Rentz AM, Secnik K, Swensen AR, Revicki DA, Michelson D, et al. The link between health-related quality of life and clinical symptoms among children with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr.* 2004;25:166–74. [PubMed: 15194901]
- [57]. Bussing R, Mason DM, Bell L, Porter P, Garvan C. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *J Am Acad Child Adolesc Psychiatry.* 2010;49:595–605. [PubMed: 20494269]
- [58]. Molloy GJ, O'Carroll RE, Ferguson E. Conscientiousness and medication adherence: a meta-analysis. *Ann Behav Med.* 2014;47:92–101. [PubMed: 23783830]
- [59]. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, et al. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A.* 2011;108:2693–8. [PubMed: 21262822]
- [60]. Caspi A, EWB, Moffitt TE, Silva PA. Early failure in the labor market: childhood and adolescent predictors of unemployment in the transition to adulthood. *Am Sociol Rev.* 1998;63:424–51.
- [61]. White JL, Moffitt TE, Caspi A, Bartusch DJ, Needles DJ, Stouthamer-Loeber M. Measuring impulsivity and examining its relationship to delinquency. *J Abnorm Psychol.* 1994;103:192–205. [PubMed: 8040489]
- [62]. Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry.* 1986;43:255–62. [PubMed: 3954545]
- [63]. Newcorn JH, Spencer TJ, Biederman J, Milton DR, Michelson D. Atomoxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44:240–8. [PubMed: 15725968]
- [64]. Batra AS, Alexander ME, Silka MJ. Attention-deficit/hyperactivity disorder, stimulant therapy, and the patient with congenital heart disease: evidence and reason. *Pediatr Cardiol.* 2012;33:394–401. [PubMed: 22298228]
- [65]. Marino BS, Shera D, Wernovsky G, Tomlinson RS, Aguirre A, Gallagher M, et al. The development of the pediatric cardiac quality of life inventory: a quality of life measure for children and adolescents with heart disease. *Qual Life Res.* 2008;17:613–26. [PubMed: 18347927]
- [66]. Uzark K, King E, Spicer R, Beekman R, Kimball T, Varni JW. The clinical utility of healthrelated quality of life assessment in pediatric cardiology outpatient practice. *Congenit Heart Dis.* 2013;8:211–8. [PubMed: 22967147]

- [67]. Agnihotri K, Awasthi S, Singh U, Chandra H, Thakur S. A study of concordance between adolescent self-report and parent-proxy report of health-related quality of life in school-going adolescents. *J Psychosom Res.* 2010;69:525–32. [PubMed: 21109039]
- [68]. Hucin B, Voriskova M, Hruda J, Marek J, Janousek J, Reich O, et al. Late complications and quality of life after atrial correction of transposition of the great arteries in 12 to 18 year follow-up. *J Cardiovasc Surg (Torino).* 2000;41:233–9.
- [69]. Culbert EL, Ashburn DA, Cullen-Dean G, Joseph JA, Williams WG, Blackstone EH, et al. Quality of life of children after repair of transposition of the great arteries. *Circulation.* 2003;108:857–62. [PubMed: 12900343]
- [70]. McCormick MC, Athreya BH, Bernbaum JC, Charney EB. Preliminary observations on maternal rating of health of children: data from three subspecialty clinics. *J Clin Epidemiol.* 1988;41:323–9. [PubMed: 3351540]

Data statement

Patient enrollment occurred many years ago, and the informed consent form did not allow submission of data for public use dataset.

Subjects in this study are now being evaluated at age 26 years in an NHLBI-funded follow-up study, and we anticipate that data will be publicly available following completion of this phase of the Boston Circulatory Arrest Study.

Patient enrollment occurred many years ago, and the informed consent form did not allow submission of data for public use dataset.

Figure. Tracking of Health Status from 8 to 16 Years

Scatter plot of PsS (Panel A) and PhS (Panel B) scores at ages 8 versus 16 years. Boxplots of PsS (Panel C) and PhS (Panel D) scores depicting distribution of 16-year scores based on 8-year score tertiles.

Comparisons of PsS and PhS scores and CHQ-PF50 subscale scores of patients with D-TGA, referent healthy adolescents, and the CHQ-PF50 13- to 15-year normative sample

Table 1.

CHQ-PF50 Scale	D-TGA 8 yr (n=135)	D-TGA 16 yr (n=137)	Local referent sample (n=85)	CHQ-PF50 normative sample (n=96)	<i>P</i> value* comparing D-TGA 16 yr to D- TGA 8 yr	<i>P</i> value [†] comparing D-TGA 16 yr to referent sample	<i>P</i> value [‡] comparing D-TGA 16 yr to normative sample
PsS	50.5 ± 9.0	51.9 ± 8.7	57.2 ± 4.2	50.0 ± 8.9	0.10	<0.001	0.10
PhS	53.6 ± 6.4	53.5 ± 6.5	55.8 ± 4.9	53.0 ± 8.8	0.87	0.01	0.61
Subscales							
Physical functioning	96.5 ± 8.9	96.4 ± 9.7	97.5 ± 8.4	96.5 ± 12.8	0.78	0.37	0.92
Role/social – emotional/behavior	90.5 ± 20.7	94.4 ± 16.1	100.0 ± 0.0	92.3 ± 20.7	0.04	0.003	0.38
Role/social – physical	98.0 ± 9.3	97.2 ± 11.2	99.4 ± 4.0	92.1 ± 21.6	0.48	0.16	0.02
Bodily pain	85.3 ± 18.5	87.2 ± 18.2	86.4 ± 16.2	81.8 ± 17.9	0.27	0.97	0.03
Behavior	72.6 ± 17.3	83.4 ± 13.8	90.4 ± 9.1	76.3 ± 17.6	<0.001	<0.001	<0.001
Mental health	78.2 ± 11.3	79.9 ± 13.1	85.8 ± 7.2	76.6 ± 12.9	0.25	<0.001	0.06
Self esteem	82.9 ± 16.1	74.7 ± 20.1	84.1 ± 15.2	76.8 ± 15.1	<0.001	0.006	0.39
General health perceptions	68.3 ± 16.2	70.0 ± 16.2	86.6 ± 12.4	72.8 ± 14.6	0.28	<0.001	0.17
Parent impact – emotional	74.9 ± 21.7	74.2 ± 22.7	88.6 ± 12.0	77.3 ± 21.4	0.70	<0.001	0.30
Parent impact – time	88.8 ± 17.3	91.5 ± 16.3	96.5 ± 11.9	85.4 ± 20.9	0.10	0.03	0.01

Values are mean ± standard deviation.

* *P* values were determined by paired-sample *t* tests.

[†] *P* values were determined by linear regression adjusting for age at CHQ assessment, sex, and concurrent social class.

[‡] *P* values were determined by two-sample *t* tests.

Higher scores are better for all summary and subscale measures.

Table II.

Relationships of neurodevelopmental outcomes of adolescents with D-TGA at 16 years with concurrent PsS and PhS scores

Neurodevelopmental outcomes 16 yr	PsS scores 16 yr	PhS scores 16 yr
Achievement		
WIAT-II Reading Composite	0.14 (0.11)	0.14 (0.10)
WIAT-II Math Composite	0.21 (0.02)	0.20 (0.02)
WIAT-II Listening Comprehension	0.19 (0.03)	0.23 (0.006)
Memory		
CMS General Memory	0.24 (0.005)	0.26 (0.003)
Visual-Perceptual Skills		
TVPS-R Visual Closure	0.19 (0.03)	0.18 (0.04)
TVPS-R Composite	0.14 (0.10)	0.17 (0.05)
Attention		
CADS-P ADHD Index T	-0.62 (<0.001)	-0.07 (0.39)
CADS-A ADHD Index T	-0.43 (<0.001)	-0.08 (0.39)
Executive Function		
BRIEF Global Executive Composite	-0.66 (<0.001)	-0.07 (0.41)
BRIEF-SR Global Executive Composite	-0.39 (<0.001)	-0.11 (0.21)
Social Intelligence		
Reading the Mind in the Eyes Test	0.20 (0.03)	0.09 (0.31)
Autism Spectrum Quotient	-0.33 (<0.001)	-0.09 (0.33)

Values are partial Pearson r (P value).

P values were determined by partial Pearson correlation coefficients adjusting for concurrent social class.

Lower scores are better for the attention and executive function tasks as well as the Autism Spectrum Quotient. Higher scores are better for all other tasks.

WIAT-II = Wechsler Individual Achievement Test, Second Edition; CMS = Children's Memory Scale; TVPS-R = Test of Visual-Perceptual Skills – Revised; CADS-P = Conners' ADHD/DSM-IV Scales – Parent; CADS-A = Conners' ADHD/DSM-IV Scales – Adolescent; BRIEF = Behavior Rating Inventory of Executive Function – Parent; BRIEF-SR = Behavior Rating Inventory of Executive Function – Self-Report.

Table III.

Relationships of neurodevelopmental outcomes of children with D-TGA at 8 years with their future PsS and PhS scores at 16 years

Neurodevelopmental outcomes 8 yr	PsS scores 16 yr	PhS scores 16 yr
Intelligence		
WISC-III		
Verbal IQ	0.21 (0.02)	0.11 (0.21)
Performance IQ	0.11 (0.19)	0.14 (0.10)
Full-Scale IQ	0.19 (0.03)	0.14 (0.11)
Achievement		
WIAT-II Reading Composite	0.14 (0.10)	0.09 (0.30)
WIAT-II Math Composite	0.13 (0.14)	0.11 (0.19)
Verbal Fluency		
Verbal Fluency Task: Sum of F, A, S	0.08 (0.36)	0.17 (0.06)
Attention		
CPRS		
Restless-Disorganized T	-0.39 (<0.001)	-0.11 (0.23)
Hyperactive-Immature T	-0.41 (<0.001)	-0.13 (0.13)
CTRS		
Hyperactivity T	-0.24 (0.008)	-0.08 (0.37)
Daydream-Attention Problem T	-0.25 (0.005)	-0.01 (0.89)
CBCL: Attention Problems T	-0.41 (<0.001)	-0.26 (0.003)
TRF: Attention Problems T	-0.30 (<0.001)	-0.09 (0.31)
ToVA (Average of Times 1 & 2)		
Omission	-0.17 (0.05)	-0.08 (0.36)
Commission	-0.09 (0.30)	0.08 (0.40)
Response Time	-0.19 (0.04)	-0.09 (0.33)
Variability	-0.15 (0.10)	0.06 (0.49)
Executive Function		
Wisconsin Card Sort Test Perseverative Errors	0.16 (0.07)	-0.01 (0.87)
Trail-Making Test: Change in Time to Complete	-0.16 (0.06)	-0.15 (0.08)

Values are partial Pearson r (P value).

P values were determined by partial Pearson correlation coefficients adjusting for social class at 8 years.

Lower scores are better for the attention and executive function tasks. Higher scores are better for all other tasks.

WISC-III = Wechsler Intelligence Scale for Children, Third Edition; WIAT-II = Wechsler Individual Achievement Test, Second Edition; CPRS = Conners' Parent Rating Scales; CTRS = Conners' Teacher Rating Scales; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; ToVA = Tests of Variables of Attention.

Table IV (Online).

Relationships of neurodevelopmental outcomes of children with D-TGA at 8 years with concurrent PsS and PhS scores

Neurodevelopmental outcomes 8 yr	PsS scores 8 yr	PhS scores 8 yr
Intelligence		
WISC-III		
Verbal IQ	0.15 (0.08)	0.15 (0.08)
Performance IQ	0.15 (0.09)	0.11 (0.19)
Full-Scale IQ	0.16 (0.06)	0.15 (0.08)
Achievement		
WIAT-II Reading Composite	0.17 (0.06)	0.07 (0.44)
WIAT-II Math Composite	0.16 (0.06)	0.14 (0.12)
Verbal Fluency		
Verbal Fluency Task: Sum of F, A, S	0.16 (0.06)	0.09 (0.32)
Attention		
CPRS		
Restless-Disorganized T	-0.68 (<0.001)	-0.07 (0.43)
Hyperactive-Immature T	-0.62 (<0.001)	-0.05 (0.55)
CTRS		
Hyperactivity T	-0.43 (<0.001)	-0.04 (0.64)
Daydream-Attention Problem T	-0.35 (<0.001)	-0.07 (0.46)
CBCL: Attention Problems T	-0.65 (<0.001)	-0.21 (0.02)
TRF: Attention Problems T	-0.44 (<0.001)	-0.16 (0.09)
ToVA (Average of Times 1 & 2)		
Omission	-0.19 (0.03)	-0.01 (0.95)
Commission	-0.06 (0.54)	0.17 (0.05)
Response Time	-0.24 (0.006)	-0.15 (0.09)
Variability	-0.13 (0.15)	0.09 (0.34)
Executive Function		
Wisconsin Card Sort Test Perseverative Errors	-0.01 (0.90)	0.14 (0.10)
Trail-Making Test: Change in Time to Complete	-0.14 (0.10)	-0.08 (0.36)

Values are partial Pearson r (P value).

P values were determined by partial Pearson correlation coefficients adjusting for concurrent social class.

Lower scores are better for the attention and executive function tasks. Higher scores are better for all other tasks.

WISC-III = Wechsler Intelligence Scale for Children, Third Edition; WIAT-II = Wechsler Individual Achievement Test, Second Edition; CPRS = Conners' Parent Rating Scales; CTRS = Conners' Teacher Rating Scales; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; ToVA = Tests of Variables of Attention.