Impact of Congenital Heart Surgery on Neurodevelopment in Children with Down Syndrome: The CHILD-DS Study

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Background

- ~50% of children with Down syndrome (DS) have congenital heart disease (CHD).
- Complete atrioventricular septal defect (CAVSD) is most common, usually repaired in infancy.
- CHD surgery has been linked to impaired neurodevelopment (ND), but studies in children with DS have been inconsistent.
- NHLBI-funded Pediatric Heart Network (PHN) Residual Lesion Score (RLS) study assembled a cohort of 1,149 infants undergoing congenital heart surgery; the trans-NIH INCLUDE Project-funded Congenital Heart disease: Impact on Learning and Development in Down Syndrome (CHILD-DS), was ancillary to RLS.

Objective

- To bridge gaps in knowledge about the impact of CHD repaired in infancy on ND and behavioral outcomes in school-aged children with DS.

Methods

- **Setting:** 14 PHN clinical sites in U.S. & Canada, May 2022-Oct 2023.
- **Participants:** 259 children 5-12 years with DS (124 CAVSD repair and 135 non-CHD)
- **Co-primary outcomes:**
  - Ratio intelligence quotients (IQs) on Stanford Binet Intelligence Scales, 5th Ed. (SB-5), calculated by dividing age-equivalent by chronological age for SB-5 domains.
  - Adaptive composite scores from Vineland Adaptive Behavior Scales, 3rd Ed.
- **Secondary outcomes:**
  - Receptive and expressive language from Peabody Picture Vocabulary Test, 5th Edition (PPVT-5) and Expressive Vocabulary Test, Third Edition (EVT-3).
  - Emotional and behavioral functioning scores on the Aberrant Behavior Checklist, 2nd Edition (ABC-2).
  - Social functioning on Social Communication Questionnaire (SCQ) and Repetitive Behavior Scale, Revised (RBS-R).
- **Statistical analysis:** Group differences tested using chi-squared or Fisher's exact tests (categorical data), t-tests or Wilcoxon signed-rank tests (continuous data). Multivariable regression models adjusted for *a priori* socio-demographic and medical history variables.

Table 1. Sample Characteristics

Median (Q1, Q3) or n (%)	Overall (n=259)	CAVSD Repair Group (n=124)	Non-CHD Group (n=135)	P
Age at consent (years)	7.7 (6.5, 9.2)	7.6 (6.5, 10.3)	7.6 (6.5, 8.7)	0.38
Male	128 (49%)	63 (51%)	65 (48%)	0.67
Race				0.09
White/Caucasian	187 (72%)	87 (70%)	100 (74%)	
Black/African American	28 (11%)	19 (15%)	9 (7%)	
Asian	9 (3%)	3 (2%)	6 (4%)	
Other or multiracial	31 (12%)	12 (10%)	19 (14%)	
Ethnicity				0.05
Hispanic or Latino/Latina	37 (14%)	12 (10%)	25 (19%)	
Not Hispanic or Latino/Latina	217 (84%)	109 (88%)	108 (80%)	
Socioeconomic status index*	0.1 (-0.5, 0.5)	-0.1 (-0.7, 0.4)	0.2 (-0.4, 0.6)	0.01

*Neighborhood SES was calculated using a modified Winkleby/Cubbin index.

Results

Cognition (SB-5)

- Cognitive skills did not differ between groups.
- ~1/3 of children scored at the floor of the test, with a full scale IQ of 10 and ratio IQs unable to be calculated, equally distributed between study groups.

Table 2. Stanford Binet-5 Cognitive Outcomes by Study Group

Median (Q1, Q3), Mean ± SD, or n (%)	Overall (n=236*)	CAVSD Repair Group (n=112)	Non-CHD Group (n=124)	P
Non-verbal Ratio IQ	38.9 (31.7, 48.2)	39.5 (31.9, 48.2)	38.8 (31.7, 47.9)	0.81
Verbal Ratio IQ	37.5 ± 10.3	37.8 ± 9.7	37.3 ± 10.9	0.73
Standard scores				
Full Scale IQ (FSIQ)	42 (10, 47)	42 (10, 48)	42 (10, 46)	0.66
FSIQ = 10	77 (33%)	40 (36%)	37 (30%)	0.34
Fluid reasoning	47 (47, 50)	47 (47, 50)	47 (47, 50)	0.79
Knowledge	52 (49, 60)	52 (49, 59)	55 (49, 60)	0.35
Quantitative reasoning	50 (50, 59)	50 (50, 59)	50 (50, 59)	0.84
Visual spatial	48 (48, 53)	48 (48, 53)	48 (48, 53)	0.54
Working memory	48 (48, 53)	48 (48, 53)	48 (48, 53)	0.86

*n's provided are for children with data deemed valid by the neurodevelopmental evaluator.

Adaptive Skills (Vineland)

- Children with CAVSD repair had lower Vineland adaptive scores in multivariable analysis.
- Group differences were seen across adaptive composite scores, domains, and communication-related subdomains.

Table 3. Vineland Adaptive Behavior Score Differences in Children with Down syndrome in the CAVSD Repair vs. Non-CHD Groups (n=233*)

	β (SE)**	P
Adaptive Behavior Composite	-3.8 (1.7)	0.03
Communication Domain	-5.3 (2.4)	0.03
Daily Living Skills Domain	-4.1 (1.9)	0.03
Socialization Domain	-4.4 (2.3)	0.05
Motor Skills Domain	-3.9 (1.8)	0.03
Receptive Subdomain	-1.0 (0.6)	0.08
Expressive Subdomain	-1.1 (0.5)	0.04

*n provided is for children with data deemed valid by the neurodevelopmental evaluator.
**Multivariable regression results, adjusting for *a priori* covariates. Group effect is presented from each model.

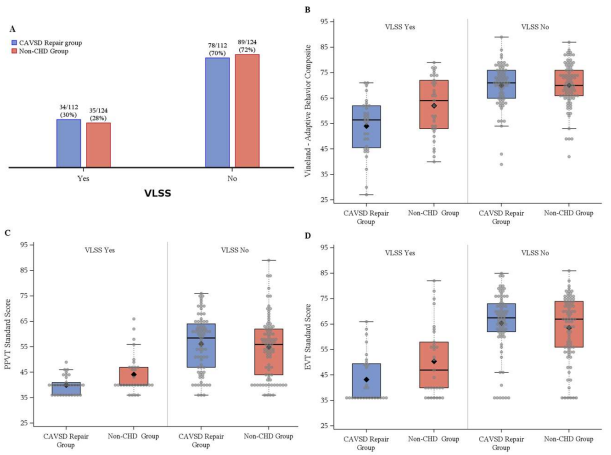
Language, Behavior, and Social Communication

- Children with CAVSD repair were less likely to pass teaching items on the EVT-3 (22% vs. 12%, P=0.03).
- Social communication as measured by SCQ total score was higher (worse) for CAVSD group (2.3±1.2 points; P=0.05).

Subset with Lowest Cognitive Scores (Post-hoc Interaction Testing)

- In total, 69 children (34 CAVSD, 35 non-CHD) could not have a ratio IQ score due to developmental age levels falling below SB-5 floor in ≥ 3 of the 5 domains.
  - This very low SB-5 score (VLSS) subset was younger (median age 6.7 vs. 8 years, P<0.001, although lower age did not drive the interaction effects) and more likely to be boys (64% vs. 44%, P=0.01) and have lower SES (median index -0.41 vs. 0.14, P=0.02).
  - Within VLSS, those with CAVSD repair had lower scores in adaptive skills, expressive and receptive language, than the non-CHD group.

Figure. ND Test Scores by Study Group & Very Low Stanford Binet Score Group



Limitations/Future Directions

- Floor effects on the SB-5 prevented calculation of ratio IQs and yielded FSIQs of 10 in both study groups, reducing power to describe and compare cognitive skills.
- Next steps are to compute deviation scores, to better capture cognitive skills for children at the testing floor.
- Additional validated testing/scoring approaches are needed to capture the full range of cognitive skills in children with DS.

Conclusions

- In school-age children with DS, those who had infant CAVSD repair had lower adaptive behavior, but no difference in cognitive scores, vs. non-CHD group.
- Children in the CAVSD repair group had more difficulty on expressive language tests and higher reports of challenges with social communication.
- Among children with lowest measured cognitive skills, those with CAVSD repair exhibited the greatest risk for impaired ND across language and adaptive skills.
- Findings contribute to understanding ND profiles of children with DS with infant CAVSD repair and identifying those who may need more developmental support.

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