Self-reported functional health status following interrupted aortic arch repair: A Congenital Heart Surgeons' Society Study

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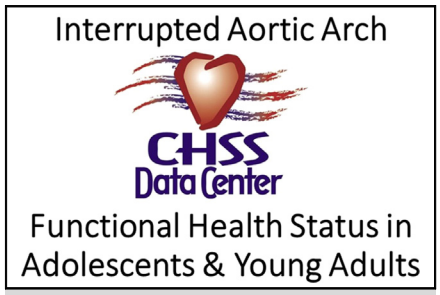
ABSTRACT

Objectives: Improved survival after congenital heart surgery has led to interest in functional health status. We sought to identify factors associated with self-reported functional health status in adolescents and young adults with repaired interrupted aortic arch.

Methods: Follow-up of survivors (aged 13-24 years) from a 1987 to 1997 inception cohort of neonates included completion of functional health status questionnaires (Child Health Questionnaire-CF87 [age <18 years, n = 51] or the Short Form [SF]-36 [age ≥18 years, n = 66]) and another about 22q11 deletion syndrome (22q11DS) features (n = 141). Factors associated with functional health status domains were determined using multivariable linear regression analysis.

Results: Domain scores of respondents were significantly greater than norms in 2 of 9 Child Health Questionnaire-CF87 and 4 of 10 SF-36 domains and only lower in the physical functioning domain of the SF-36. Factors most commonly associated with lower scores included those suggestive of 22q11DS (low calcium levels, recurrent childhood infections, genetic testing/diagnosis, abnormal facial features, hearing deficits), the presence of self-reported behavioral and mental health problems, and a greater number of procedures. Factors explained between 10% and 70% of domain score variability (R^2 = 0.10-0.70, adj-R^2 = 0.09-0.66). Of note, morphology and repair type had a minor contribution.

Conclusions: Morbidities associated with 22q11DS, psychosocial issues, and recurrent medical issues affect functional health status more than initial morphology and repair in this population. Nonetheless, these patients largely perceive themselves as better than their peers. This demonstrates the chronic nature of interrupted aortic arch and suggests the need for strategies to decrease reinterventions and for evaluation of mental health and genetic issues to manage associated deteriorations. (J Thorac Cardiovasc Surg 2019;157:1577-87)



Functional health status in adolescents and young adults with interrupted aortic arch.

Central Message

Morbidities associated with 22q11, psychosocial issues, and recurrent medical issues strongly affect functional health status in survivors of IAA; however, these survivors largely perceive themselves as better than their peers.

Perspective

We continue to demonstrate that IAA is a chronic disease and suggest the need for strategies to decrease reinterventions and to evaluate mental health and genetic issues. Longitudinal functional health status evaluation is also needed to ascertain changes related to increasing medical complexity, admissions and procedures, and those associated with mature adult roles and responsibilities.

See Commentaries on pages 1588 and pages 1590.

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Abbreviations and Acronyms

22q11DS = 22q11 deletion syndrome
CHD = congenital heart disease
CHQ-CF87 = Child Health Questionnaire (CHQ) Version CF-87
CHSS = Congenital Heart Surgeons' Society
FHS = functional health status
IAA = interrupted aortic arch
SF-36 = Short Form (36) Health Survey version 2

Scanning this QR code will take you to the article title page to access supplementary information.

Outcomes in children with interrupted aortic arch (IAA) have been conventionally measured by using the metrics of survival and perioperative morbidity and mortality. As outcomes improve, survivors now have a greater expectation of longevity after repair, making morbidity and mortality measurements inadequate. Therefore, functional health status (FHS) has become an important outcome measure, as we assess how these patients fare as adolescents and adults, especially compared with those without disease.

FHS can be defined as the amount of disability a patient experiences secondary to his/her health care condition with regard to any domain in their life. It represents the ability of an individual to perform normal activities, such that they can fulfill basic needs, perform usual roles, and support both health and well-being.[1,2] FHS instruments allow us to measure these domains of health and assess the impact of disease on a patient's life.

Previous studies of FHS in pediatric cardiac surgery survivors using questionnaires have displayed considerable variability, with domains scores showing lower,[3-9] comparable,[6,8-13] or even greater scores relative to population norms.[6,8,9,14] However, many of these studies were based on parent-reported FHS, rather than self-reported FHS. Recent literature has focused on the perceptions of the patient (self-reports) as opposed to proxies, or has compared patient and proxy results.[4,6-8,10,11,13] Using 2 of these nondisease-specific FHS questionnaires, the Child Health Questionnaire (CHQ) Version CF-87 (CHQ-CF87) and the Short Form (36) Health Survey version 2 (SF-36), the Congenital Heart Surgeons' Society (CHSS) sought to assess the late self-reported FHS of patients after IAA repair and the patient-specific factors associated with scores in each domain.[15]

The goals of the analysis were to: (1) compare the FHS of patients with IAA with normative data, (2) determine whether adolescent or adult IAA populations have more deviation from normative data, (3) determine the proportion of patients demonstrating features related to 22q11 deletion syndrome (22q11DS) status (DiGeorge syndrome), and (4) determine the patient, clinical (including features related to 22q11DS status), and socioeconomic characteristics associated with scores of the different domains of the FHS questionnaires.

METHODS

Patients and Questionnaires

Between January 1987 and December 1997, patients with IAA admitted to a CHSS institution within 30 days of birth were prospectively enrolled by 29 CHSS member institutions (Appendix E1). IAA was defined via the operative note as a complete discontinuity or a nonpatent fibrous strand in the transverse arch or aortic isthmus. Patients who did not undergo arch repair were excluded (ie, died preintervention, aborted procedure, palliation, transplant). Medical and surgical management strategies were selected by the enrolling institution based on surgeon and institutional experience and preference.

During annual cross-sectional follow-up (08/09-08/10), a copy of the CHQ-CF87 was sent to all surviving patients <18 years old and the SF-36 to all surviving patients ≥18 years old at the time of the mailing. All patients also received a questionnaire developed by the CHSS related to current 22q11DS status and features. If no response was received within 6 weeks of initial mailing, a reminder was mailed, followed by 2 attempts to complete telephone follow-up, in addition to reminder e-mails if addresses were available.

For a flow chart of patients in the study, see Figure 1. Note 22 questionnaires were primarily completed by caregivers, secondary to inability of the patient to complete the questionnaire, potentially, but not necessarily indicating cognitive impairment. These were excluded. As a result, our study included 117 of 278 patients (42%) at a median age of 19 years (range 13-23, and mean age 19 ± 3 years). We also had 141 of 278 (51%) patients return a 22q11DS questionnaire (2 patients who completed the CHQ-CF87 and 3 who completed the SF-36, did not complete the 22q11DS questionnaire; in addition, some patients' families only completed the 22q11DS questionnaire). Patient characteristics and cardiac morphology (responders and nonresponders) are summarized in Appendix E2.

CHQ-CF87 and SF-36

Both the CHQ-CF87 and the SF-36 are highly validated patient completed questionnaires focusing on an individual's subjective perception of his/her health, as opposed to parental perceptions.[16-20] In both questionnaires, greater domain scores indicate better self-perceived function. In both questionnaires, respondents are also asked to rate their change in health in comparison with 1 year ago. Of note, the SF-36 contains 2 psychometrically based scores, the Physical Component Summary and the Mental Component Summary, which are calculated from the domain scores within the SF-36. Table 1 presents the features of the CHQ-CF87 and SF-36.

22q11DS Questionnaire

The CHSS qualitative 22q11DS questionnaire was developed to assist us in determining whether patients exhibit any of the features commonly associated with 22q11DS, despite a recorded diagnosis

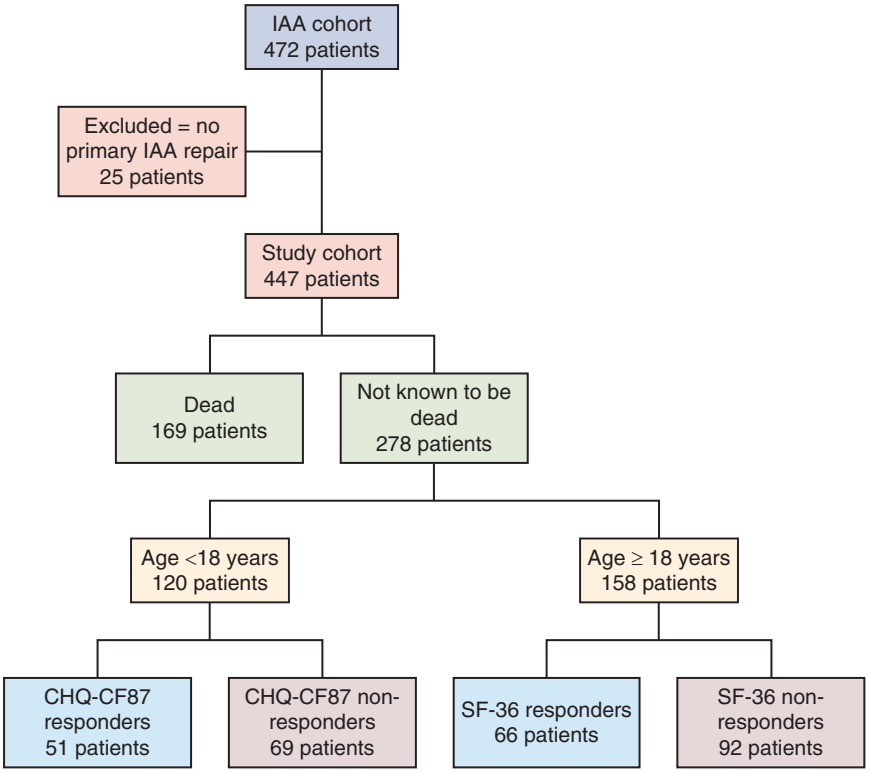


FIGURE 1. Flow chart of patients in study. *IAA*, Interrupted aortic arch; *CHQ-CF87*, Child Health Questionnaire-Child Form 87; *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2.

(see Appendix E3 for the details regarding questionnaire development and validation of the questionnaire, raw response data, and a summary of findings). When many patients were initially diagnosed and evaluated for IAA, genetic testing was not widely available, and because of the variable phenotype associated with 22q11DS, many patients may not have been diagnosed clinically with this condition.

TABLE 1. Features of the CHQ-CF87 and the SF-36 questionnaires

	CHQ-CF87	SF-36
Focus	Generic	Generic
Number of items (questions)	87	36
Age, y	10 to <18	≥18
Number of domains	13	8
Score	Range 0-100	50 is the average score or norm
Number of psychometrically-based scores (calculated from the other domains)	0	2
Names of psychometrically-based scores	N/A	Physical Component Summary Mental Component Summary
Domains used to calculate each psychometrically based score	N/A	Physical Component Summary Physical Functioning Role-Physical (freedom from) Bodily Pain General Health Mental Component Summary Vitality Social Functioning Role-Emotional Mental Health

CHQ-CF87, Child Health Questionnaire-Child Form 87; *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2; *N/A*, not available.

Additional Data Collection

See Appendix E4.

Consent

Informed consent was obtained from patients. Ethics approval for the CHSS was obtained from the Research Ethics Board at SickKids, in addition to obtaining local institutional approval. Institutional review board approval number, initial study approval date, and expiration date are 0019990052, October 27, 2009/November 5, 2009, and March 13, 2019, respectively.

Statistical Analysis

Standard descriptive and comparative statistics were performed. Z scores were calculated for both FHS questionnaires to examine deviations from normal and assess degree of deviation between adolescents and young adults. FHS scores were compared with normative data using single sample *t* tests against a hypothesized mean. Multivariable linear regression with bootstrap bagging was performed using selected variables in Appendix E2 and the 22q11DS questionnaire. Missing data were imputed using the technique of mean imputation. Final multivariable models for each FHS score were obtained through stepwise multivariable regression modeling, with backward selection of the variables selected using bootstrapping.

See Appendix E4[20-22] for detailed information regarding consent and the statistical methods.

RESULTS

Comparison With Normative Data

CHQ-CF87 scores were significantly different in 2 of 9 categories when compared with normative data, with a greater score for Mental Health ($P = .03$) and for (freedom from) Bodily Pain ($P < .0001$) (Table 2, Figure 2, *A*). Patients who underwent the SF-36 were compared with normative patients aged 18 to 24 years (Table 2, Figure 2, *B*). SF-36 responders were found to have greater scores for 4 of 10 domains, specifically the Mental Component Summary ($P = .04$), (freedom from) Bodily Pain ($P = .0002$), Vitality ($P = .0002$), and Mental Health ($P = .01$). Patient scores were only significantly

TABLE 2. Questionnaire scores with published norms and z scores

CHQ-CF 87 domains	IAA patients <18 y (n = 51), mean ± standard deviation, m = missing	Published norms, n = 232	*P* value	Z score
Global Health (GGH)	77.2 ± 17.2, m = 2	–	–	–
Physical Functioning (PF)	86.6 ± 15.6, m = 1	88.8 ± 14.0	.3	–0.2
Role/Social Limitations-Emotional (RE)	85.6 ± 20.7, m = 1	85.9 ± 21.0	.9	–0.02
Role/Social Limitations-Behavioral (RB)	88.0 ± 25.3, m = 2	86.5 ± 21.5	.7	0.07
Role/Social Limitations-Physical (RP)	92.3 ± 16.7, m = 2	88.3 ± 21.0	.1	0.2
(Freedom from) Bodily Pain (BP)	87.8 ± 19.3, m = 1	74.4 ± 23.1	<.0001	0.6
Behavior (BE)	73.0 ± 16.5, m = 1	76.6 ± 14.6	.1	0.1
Global Behavior (GBE)	71.0 ± 27.6, m = 0	–	–	–
Mental Health (MH)	77.6 ± 15.2, m = 1	72.7 ± 16.0	.03	0.7
Self Esteem (SE)	79.3 ± 15.6, m = 2	81.8 ± 15.8	.3	0.3
General Health Perceptions (GH)	64.5 ± 14.8, m = 2	66.4 ± 14.6	.4	0.3
Family Activities (FA)	80.0 ± 23.8, m = 2	–	–	–
Family Cohesion (FC)	73.9 ± 22.6, m = 3	–	–	–
SF-36 domains	**IAA patients >18 y (n = 66), mean ± standard deviation, m = missing**	**Published norms males and females ages 18-24 y, n = 216 except Mental Health where n = 215**	***P* value**	**Z score**
Physical Component Summary (PF/RP/BP/GH)	52.4 ± 7.5, m = 3	53.5 ± 9.2	.3	–0.1
Mental Component Summary (VT/SF/RE/MH)	49.3 ± 12.0, m = 3	46.1 ± 13.3	.04	0.2
Physical Functioning (PF)	50.7 ± 8.0, m = 1	53.2 ± 9.7	.02	–0.3
Role-Physical (RP)	50.9 ± 8.6, m = 1	52.8 ± 9.6	.09	–0.2
(Freedom from) Bodily Pain (BP)	55.9 ± 8.0, m = 1	52.0 ± 10.6	.0002	0.4
General Health (GH)	49.2 ± 10.9, m = 2	49.7 ± 11.8	.7	–0.04
Vitality (VT)	52.6 ± 11.3, m = 2	47.0 ± 11.7	.0002	0.5
Social Functioning (SF)	49.1 ± 10.0, m = 2	49.2 ± 12.3	.9	–0.009
Role-Emotional (RE)	49.0 ± 11.8, m = 2	49.8 ± 12.5	.6	–0.06
Mental Health (MH)	50.7 ± 11.8, m = 2	46.9 ± 13.0	.01	0.3

CHQ-CF87, Child Health Questionnaire-Child Form 87; *IAA*, interrupted aortic arch; *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2.

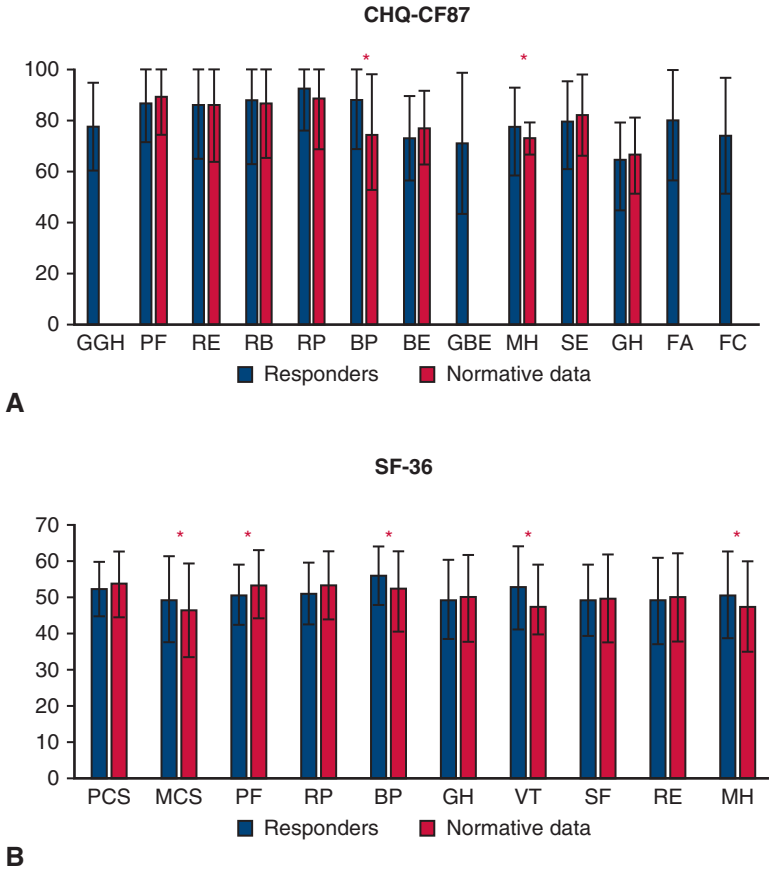


FIGURE 2. Comparison of CHQ-CF87 and SF-36 data to normative data. A, Comparison for CHQ-CF87. *CHQ-CF87*, Child Health Questionnaire-Child Form 87; *GGH*, Global Health; *PF*, Physical Functioning; *RE*, Role/Social Limitations-Emotional; *RB*, Role/Social Limitations-Behavioral; *RP*, Role/Social Limitations-Physical; *BP*, (Freedom from) Bodily Pain; *BE*, Behavior; *GBE*, Global Behavior; *MH*, Mental Health; *SE*, Self-Esteem; *GH*, General Health Perceptions; *FA*, Family Activities; *FC*, Family Cohesion. B, Comparison for SF-36. *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2; *PCS*, Physical Component Summary; *MCS*, Mental Component Summary; *RP*, Role-Physical; *GH*, General Health Perceptions; *RE*, Role-Emotional; *VT*, Vitality; *SF*, Social Functioning.

lower for the Physical Functioning domain of the SF-36 ($P = .02$).

Comparisons of Z Scores With Normative Data

There are 2 of 9 categories from the CHQ-CF87 in which the z scores were negative (Physical Functioning and Role/Social Limitations-Emotional), whereas the remainder were positive (7 of 9). However, only 2 of these have statistically significant P values ([freedom from] Bodily Pain [$P < .0001$] and Mental Health [$P = .03$]). In contrast, when we examined the SF-36 scores, the majority of categories (6 of 10) have a slight trend to being below the normal values, and only 5 are statistically significantly different (with only Physical Functioning having a negative z score) (Table 2).

Change in Health Status Compared With 1 Year Ago

On both questionnaires, health status is graded using 5 choices. For both questionnaires, the majority of patients reported that their health is about the same now as 1 year ago (55% and 72% respectively), with more CHQ-CF87 patients doing worse (36% [18/49]), and more SF-36 patients doing better (25% [16/65]) compared with 1 year ago (Table 3).

Domain Associations for FHS Questionnaires

Multivariable regression analyses were performed for each CHQ-CF87 and SF-36 domain score (Tables 4 and 5), and are further described herein. Although statistically significant, the percentage variation in CHQ-CF87 and SF-36 domain scores explained by the factors was highly variable, with adjusted R^2 values ranging from 13% to 66% for the CHQ-CF87 and 9% to 51% for the SF-36. Of note, FHS was minimally related to IAA morphology and repair type.

CHQ-CF87 Domain Associations

Three main groups of variables were predominantly associated with CHQ-CF87 domains (Table 4). These were variables related to mental health, association with a genetic

TABLE 3. Health status now versus 1 year ago from both functional health status questionnaires

	CHQ-CF87 Change in health (CH) m = 2	SF-36 Reported health transition (HT) m = 1
Much better now than 1 y ago	1/49 (2%)	4/65 (6%)
Somewhat better now than 1 y ago	3/49 (6%)	12/65 (18%)
About the same now as 1 y ago	27/49 (55%)	47/65 (72%)
Somewhat worse now than 1 y ago	8/49 (16%)	1/67 (2%)
Much worse now than 1 y ago	10/49 (20%)	1/65 (2%)

The answers from both questionnaires are reported as raw data. *CHQ-CF87*, Child Health Questionnaire-Child Form 87; *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2.

condition, and those related to the total number of procedures patients underwent. The first of these groups were variables related to mental health status, specifically those from the 22q11DS questionnaire (discussed further herein). In all domains (except for Global Health, [freedom from] Bodily Pain, and General Health Perceptions), either the presence of mental health counseling or having taken medications for mental health problems was associated with decreased scores. The next group of variables related to genetic testing or the presence of a genetic condition and were also taken from the 22q11DS questionnaire. These variables also greatly affected scores and were associated with lower scores in the domains of (freedom from) Bodily Pain, Behavior, Self Esteem, and Family Activities. The third group of variables was the total number of procedures (''other'' or catheter-based interventional), with more procedures being associated with lower domain scores. This was associated with Global Health, Role/Social Limitations-Physical, Mental Health, and Self Esteem.

Multiple other variables were significantly associated with CHQ-CF87 domain scores (Table 4). Of note, lower median neighborhood family income (calculated in US dollars) was adversely associated with the domains of Family Activities and Family Cohesion (ie, this was associated with lower scores). Features of 22q11DS (abnormal facial features, taking calcium supplements, having low calcium levels, having had speech therapy, having abnormal hearing, and having recurrent infections) were also associated with lower scores.

SF-36 Domain Associations

When we examined the results of the SF-36, 2 of the 3 groups of variables described above were widely associated with many domains of the SF-36 questionnaire (variables related to poor mental health and greater total number of procedures) (Table 5). Variables related to mental health taken from the 22q11DS questionnaire were associated with lower scores in 4 of the domains ([freedom from] Bodily Pain, Vitality, Social Functioning, and Mental Health), and the Mental Component Summary score. As with the CHQ-CF87, a greater total number of procedures (arch, left ventricular outflow tract, or procedure of any type) was again associated with poorer scores in many domains. Shorter time to the last procedure was associated with poorer domain scores for Social Functioning and the Mental Component Summary score.

Several other features from the 22q11DS questionnaire were associated with lower scores, including recurrent childhood infections requiring medication or admission to hospital with the General Health domain, having a history of a low calcium level with the (freedom from) Bodily Pain domain, and having had behavioral problems in school with the Role-Emotional domain.

Finally, several other variables were associated with lower scores in various domains of the SF-36. These include the association of a lower median family income with the Physical Functioning and Role-Physical domain; presence of uncomplicated IAA with (freedom from) Bodily Pain and Social Functioning domain; lower weight at index repair with the Social Functioning domain; greater total number of medications with the Role-Emotional domain; and finally, younger age at questionnaire completion was adversely associated with the Mental Component Summary.

Findings From the 22q11DS Questionnaire

Please see Appendix E3 for findings from the 22q11DS questionnaire.

Comparison of Responders With Nonresponders

Although there were not many differences between responders and nonresponders for the CHQ-CF87, responders were less likely to have ''other'' medical problems (27% vs 51%, $P = .01$), had greater total number of surgical procedures (1.98 ± 1.05 vs 1.51 ± 0.72, $P = .01$), and were more likely to have reoperative procedures with circulatory arrest (27% vs 10%, $P = .01$). The only difference between SF-36 responders and nonresponders is that responders were younger (19.9 ± 1.3 vs 20.5 ± 1.7 years, $P = .05$). See Appendix E2 for a complete list of the variables compared.

DISCUSSION

Summary

Our study of FHS demonstrates that patients with IAA generally perceive themselves as the same or better than their normal peers in multiple domains. The presence of factors related to the total number of procedures, time since last procedure, mental health, genetic testing or diagnosis, features potentially related to 22q11DS, and lower family income dominated over those related to anatomical details, repair type, and other variables. This suggests that variables associated with a recurrent well-being or health care interaction burden (eg, total number of procedures) or more

TABLE 4. Summary of multiple regression analysis for independent factors associated with lower scores on individual domains for the Child Health Questionnaire-Child Form 87

Variable	Parameter estimate	*P* value	Reliability	R^2/adjR^2
Global Health (GGH)				0.17/0.14
Questionnaire reports that patient has been told by a doctor that he/she has abnormal facial features	12.11 ± 5.11	.02	80%	
Greater total number of "other" procedures	7.06 ± 3.45	.05	50% by cluster	
Physical Functioning (PF)				0.52/0.48
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	16.20 ± 3.63	<.0001	83%	
Questionnaire reports patient taking calcium supplements or medications to correct calcium levels	13.45 ± 5.02	.01	61%	
Greater total number of medications	5.27 ± 1.35	.0003	76%	
Questionnaire reports that patient has had low calcium levels	20.65 ± 4.54	>.0001	62%	
Lower weight at index IAA repair, kg (squared)	5.63 ± 2.00	.007	59% by cluster	
Role/Social Limitations-Emotional (RE)				0.16/0.15
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	17.20 ± 5.56	.003	63%	
Role/Social Limitations-Behavioral (RB)				0.15/0.13
Questionnaire reports patient taking medication for mental health problems	21.64 ± 7.47	.006	75%	
Role/Social Limitations-Physical (RP)				0.47/0.41
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	13.97 ± 3.91	.0009	76%	
Elapsed time on bypass at index repair, min (inverse)	1770.30 ± 663.18	.01	74% by cluster	
Questionnaire reports patient taking calcium supplements or medications to correct calcium levels	12.15 ± 4.73	.01	70% by cluster	
Younger at questionnaire completion, y (inverse)	863.04 ± 293.42	.005	69% by cluster	
Greater total number of catheter-based interventional procedures	6.63 ± 2.98	.03	50% by cluster	
(Freedom from) Bodily Pain (BP)				0.33/0.30
Questionnaire reports that patient has had speech therapy	22.82 ± 5.70	.0002	55%	
Questionnaire reports that patient has a current diagnosis of DiGeorge	25.20 ± 5.80	<.0001	50%	
Behavior (BE)				0.36/0.33
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	17.39 ± 3.92	<.0001	51%	
Patient reports having DNA testing	11.85 ± 4.22	.007	56% by cluster	
Global Behavior (GBE)				0.40/0.38
Questionnaire reports patient taking medication for mental health problems	33.04 ± 7.03	<.0001	55%	
Presence of other medical problems	20.36 ± 6.84	.005	54% by cluster	
Mental Health (MH)				0.70/0.66
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	18.95 ± 2.84	<.0001	94%	
Absence of an anomalous right subclavian	9.95 ± 3.00	.002	68%	
Greater total number of medications	4.76 ± 1.11	<.0001	63%	
Presence of other medical problems	12.56 ± 2.85	<.0001	61%	
Questionnaire reports having abnormal hearing test result	12.65 ± 2.99	.0001	51%	
Greater total number of catheter-based interventional procedures	8.17 ± 2.16	.0005	57% by cluster	
Self Esteem (SE)				0.40/0.37
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	13.39 ± 3.57	.0005	56%	
Questionnaire reports having a diagnosis of a genetic condition	11.79 ± 3.76	.003	65% by cluster	
Higher total number of "other" procedures	4.90 ± 1.87	.01	64% by cluster	

(Continued)

TABLE 4. Continued

Variable	Parameter estimate	*P* value	Reliability	R^2/adjR^2
General Health Perceptions (GH)				0.16/0.14
Questionnaire reports recurrent childhood infections requiring medication or admission to hospital	12.99 ± 4.23	.004	59%	
Family Activities (FA)				0.53/0.49
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	31.42 ± 5.12	<.0001	77%	
Questionnaire reports having a diagnosis of a genetic condition	18.88 ± 5.14	.0006	74% by cluster	
Lower weight at index IAA repair, kg (squared)	8.08 ± 2.95	.009	64% by cluster	
Lower median family income for (USD) neighborhood (inverse)	66.96 ± 20.97	.003	61% by cluster	
Family Cohesion (FC)				0.38/0.33
Presence of bicuspid aortic valve	32.08 ± 6.72	<.0001	82%	
Absence of an anomalous right subclavian	17.21 ± 6.55	.01	61%	
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	17.40 ± 5.64	.003	52%	
Lower median family income for neighborhood USD) (inverse)	71.35 ± 23.46	.004	65% by cluster	

IAA, Interrupted aortic arch; *USD*, United States dollars.

immediacy (eg, time since last procedure) and a greater potential impact with respect to the patient (eg, mental health) have a stronger influence on FHS. Two variables associated with poor domain scores help to confirm this; shorter time since last procedure and more procedures (which may be a surrogate for more recent procedures). See Video 1 for a summary of our study.

Comparison With Normative Data

The only domain from both questionnaires in which patients had significantly lower scores than their normal peers was Physical Functioning for the SF-36. All other domains showed no significant differences, or significantly greater scores. Similar to other studies, our patients had greater scores in the (freedom from) Bodily Pain domain (ie, less pain).[4,6,8,9,14,23] These greater scores might be secondary to many factors, including the notion that these children have increased resiliency and strength after having had an operation for congenital heart disease (CHD), or that having CHD gives children a different reference point for comparison.

Patients with IAA generally perceive themselves as having the same or greater FHS than their peers, possibly attributed to several concepts reported in the literature: the disability paradox; response shift; and sense of coherence.[24,25] The disability paradox results from a conflict in perception about these individuals with IAA. Although they are often perceived by external observers to have an undesirable daily life, they feel that they experience good FHS, as demonstrated by their scores. Response shift is the change in internal standards and values due to a redefinition of "good FHS."[26,27] Patients with IAA may have developed internal values of health that are different from healthy individuals, leading them to rate themselves the same or greater than their normal peers.[24] Finally, a sense of coherence can be defined as a gauge of an individual's view on the world, which is improved by a sense of being highly comprehensible, manageable, and meaningful.[24,28] Patients who grow up with CHD may have learned to cope with their disease (ie, have made it more manageable) and have an increased appreciation and meaningfulness associated with their life, as they have had it threatened by an illness that required major surgery.[24]

Demographic and Clinical Factors

In our multivariable analyses, adjusted R^2 values ranged from 9% to 66% ($R^2 = 0.10$-0.70), which indicates that in some cases a large part of the variation in a domain score can be explained by the variables we have tested (a high R^2), whereas in others the opposite was true (a low R^2). In a past publication by Culbert and colleagues,[14] whereby each domain was evaluated for associations, R^2 values for models for the CHQ-CF87 domains ranged from 0.024-0.26. We could not find publications reporting R^2 values for the SF-36 domains. In most domains, the variables we tested place our R^2 values toward the upper values of past ranges or above those in past publications. However, we still have not been able to find the combination of explanatory variables allowing us to explain a larger proportion of the variation. We would likely benefit from including other information in our dataset which we did not have, possibly related to current symptoms and exercise capacity.

Adolescents Compared With Adults

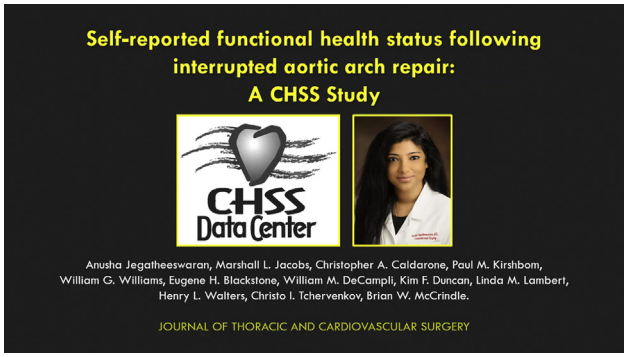
When we compare the health status of adolescents (CHQ-CF87) and young adults (SF-36), now versus 1 year ago, in adolescents a small proportion of patients seemed to be getting worse (somewhat worse or much worse), whereas in

TABLE 5. Summary of multiple regression analysis for independent factors associated with lower scores on individual domains for the Short Form-36 Health Survey

Variable	Parameter estimate	*P* value	Reliability	R^2/adjR^2
Physical Component Summary (PCS)				0.11/0.10
Greater total number of arch procedures	2.41 ± 0.85	.007	71% by cluster	
Mental Component Summary (MCS)				0.47/0.44
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	14.17 ± 2.65	<.0001	95%	
Younger age at questionnaire completion, y (inverse)	879.63 ± 371.25	.02	60% by cluster	
Shorter time since last procedure, y (inverse)	94.64 ± 28.65	.001	52% by cluster	
Physical Functioning (PF)				0.10/0.09
Lower median family income for neighborhood (USD) (inverse)	30.81 ± 11.60	.01	63% by cluster	
Role-Physical (RP)				0.17/0.15
Greater total number of arch procedures	2.93 ± 0.97	.004	59%	
Lower median family income for neighborhood (USD) (inverse)	25.52 ± 12.00	.04	61% by cluster	
(Freedom from) Bodily Pain (BP)				0.52/0.49
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	8.57 ± 1.69	<.0001	87%	
Presence of uncomplicated IAA	5.15 ± 1.87	.008	78%	
Questionnaire reports that patient has had low calcium levels	5.13 ± 1.93	.01	54%	
Greater total number of procedures of any type	1.73 ± 0.41	<.0001	63% by cluster	
General Health (GH)				0.21/0.18
Questionnaire reports recurrent childhood infections requiring medication or admission to hospital (present)	10.45 ± 3.14	.002	50%	
Greater total number of arch procedures	3.07 ± 1.20	.01	59% by cluster	
Vitality (VT)				0.32/0.31
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	14.72 ± 2.71	<.0001	94%	
Social Functioning (SF)				0.55/0.51
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	11.96 ± 2.02	<.0001	87%	
Presence of uncomplicated IAA	5.18 ± 2.27	.03	68%	
Greater total number of left ventricular outflow tract procedures	2.53 ± 1.05	.02	55% by cluster	
Lower weight at index IAA repair, kg (inverse)	57.93 ± 16.38	.0008	56% by cluster	
Shorter time since last procedure, y (inverse)	114.58 ± 22.75	<.0001	60% by cluster	
Role-Emotional (RE)				0.32/0.29
Questionnaire reports patient has had a behavioral problem in school	9.04 ± 3.41	.01	58%	
Greater total number of medications	3.17 ± 0.86	.0005	52%	
Greater total number of arch procedures	4.41 ± 1.22	.0006	80% by cluster	
Mental Health (MH)				0.34/0.33
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist, or psychiatrist	15.87 ± 2.75	<.0001	95%	

IAA, Interrupted aortic arch; *USD*, United States dollars.

young adults a small proportion was doing better (somewhat better or much better). In both groups, the majority thought their health was about the same now as 1 year ago (55% vs 72%), although the proportion was greater for young adults. For the adolescents who completed this questionnaire (12.9-17.8 years of age), we speculate that a small proportion feel that their condition is getting worse, as at their age they are more aware of differences when compared with their normal peers. We speculate that more young adults who completed the questionnaire (18.0-23.2 years of age) feel they are doing better for a similar reason of increased stability as they mature into their



VIDEO 1. Self-reported functional health status following interrupted aortic arch repair: A Congenital Heart Surgeons' Society Study. Video available at: https://www.jtcvs.org/article/S0022-5223(19)30001-7/fulltext.

adult roles. Another reason that the data may be demonstrating these differences is the young adult population may be self-selecting or evolving to represent those who are doing better or are more stable with respect to their health (attrition of sicker patients), whereas the adolescent population is still evolving.

Results from the CHQ-CF87 show only significant differences in 2 domains ([freedom from] Bodily Pain and Mental Health), in both of which patients with IAA score greater than their normal peers. In comparison, on the SF-36, patients with IAA score greater in 1 component score (Mental Component Summary) and 3 domains ([freedom from] Bodily Pain, General Health, and Mental Health), with only Physical Functioning having a significantly lower score. These results may demonstrate that adult patients with IAA tend to feel they are doing even better compared with their adolescent counterparts, although these results are not from the same questionnaire, preventing direct comparison. Only with respect to Physical Functioning do young adults fare worse; however, this may be the result of multiple causes and should be the focus of future work. We can speculate that this results from fewer patients transitioning to adult care, with transition occurring at a later age or not at all. We can also hypothesize that their poorer Physical Functioning scores may be secondary to patients not being medically optimized because they have not transitioned to adult care and are not receiving appropriate care. This may also be related to a change in perception as patients age, with patients older than 18 years of age having a different perspective than their younger counterparts with regard to normal physical functioning once they become more independent and are able to better compare themselves with their peers.

Study Limitations

The questionnaire-based limitations include the following: (1) that these questionnaires are performed in a cross-sectional fashion, and we do not know how FHS varies daily and over longer periods; (2) we have used generic questionnaires that may overlook important disease-specific measures in this population but allow for comparison with normal reference populations (we also chose to use a generic questionnaire because there was no other FHS data available on this population); (3) since both questionnaires are self-reported, cognitively impaired patients who could not complete the questionnaire were excluded, likely biasing results as these patients likely have worse FHS; and (4) the 22q11DS questionnaire was developed for use qualitatively with validation via cognitive debriefing; however, results have not been validated against a normal population. The study-based limitations and sources of bias include the following: (1) the CHSS cohort likely does not contain every patient eligible from each CHSS institution, potentially contributing to selection bias; (2) the response rate was suboptimal, although good for survey methodology, and thus results may not reflect those of the entire population (although differences were examined between responders and nonresponders); (3) CHQ-CF87 responders were less likely to have "other" medical problems, more surgical procedures, and more reoperations with circulatory arrest, potentially providing us with more current contact information and thus the ability to contact them; (4) the overall mortality in our cohort (enrolled 1987-1997) was 38% (169/447), and because mortality is better in the current era, our FHS results could also differ in a contemporary cohort[15,22,29-31]; and (5) each assessment of FHS should be appreciated as only part of a larger picture of well-being that includes more traditional outcome data and objective data such as exercise testing.

Although the denominator we used was 278 patients, 6 patients previously refused participation, and the CHSS Data Center could not directly contact 56 patients because of regulatory issues (with minimal follow-up by institutions). Thus, the denominator could have been lowered, increasing response rates.

Future Directions

Areas for extension of this work include (1) combining these data with objective FHS measures (eg, exercise test data), (2) repeated assessment of FHS to assess time/event related changes, (3) using cardiac specific questionnaires, and (4) comparison with other CHD groups to appreciate differences related to diagnosis and complexity.

CONCLUSIONS

FHS in adolescence and early adulthood is predominantly affected by morbidities associated with (but not unique to) 22q11DS, psychosocial issues, and recurrent medical procedures, rather than specific details related to underlying morphology and initial surgical repair. This supports what we established in our previous paper, that IAA is a chronic disease. However, patients with IAA also

generally perceived themselves as having the same or greater FHS than their normal peers. From a clinical perspective, strategies to reduce the need for reinterventions should be a focus of surgical efforts, as patients with recurrent medical procedures tend to fare worse with respect to FHS. In light of our findings, preoperative counseling by surgeons and cardiologists should potentially stress ongoing evaluation of genetic and mental health issues, which may be an important component of care, especially in the transition from adolescence to early adulthood. Longitudinal FHS assessment is needed via prospective repeated measurement to detect normal variation, deteriorations related to increasing medical complexity, changes associated with admissions and procedures, and variation associated with mature adult roles and responsibilities.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: congenital heart disease, CHD, CHD interrupted arch, database, outcomes, quality of life, statistics, statistics regression analysis

CONG

APPENDIX E1. PARTICIPATING CONGENITAL HEART SURGEONS' SOCIETY INSTITUTIONS

Institution name

Canada

Hospital for Sick Children, Toronto, Ontario

Montreal Children's Hospital, Montreal, Quebec

International

Heart Institute, Sao Paulo, Brazil

United States

University of Alabama at Birmingham, Birmingham, Ala

The Children's Hospital, Denver, Colo

Miami Children's Hospital, Miami, Fla

University of Miami, Miami, Fla

All Children's Hospital, St Petersburg, Fla

Loma Linda University Medical Center, Loma Linda, Calif

Children's Hospital of Los Angeles, Los Angeles, Calif

University of California, Los Angeles, School of Medicine, Center for Health Science, Los Angeles, Calif

Children's Hospital and Health Center, San Diego, Calif

University of California, San Francisco, Calif

Children's Memorial Hospital, Chicago, Ill

University of Chicago, Chicago, Ill

University of Iowa Hospitals and Clinics, Iowa City, Iowa

The Children's Hospital, Boston, Mass

Mott Hospital, Ann Arbor, Mich

Children's Hospital of Michigan, Detroit, Mich

University of Nebraska Medical Center and Children's Hospital, Omaha, Neb

Children's Hospital of Buffalo, Buffalo, NY

Columbia Presbyterian, New York, NY

Duke University Medical Center, Durham, NC

Children's Hospital Medical Center, Cincinnati, Ohio

Milton S. Hershey Medical Center, Hershey, Pa

The Children's Hospital of Philadelphia, Philadelphia, Pa

Children's Hospital of Pittsburgh, Pittsburgh, Penn

Medical University of South Carolina, Charleston, SC

Primary Children's Hospital, Salt Lake City, Utah

APPENDIX E2. Patient demographic, morphologic, and procedure-related variables for responders and nonresponders of the CHQ-CF87 and SF-36

Variable	CHQ-CF87, n = 51		CHQ-CF87 nonresponders, n = 69		*P* value	SF-36, n = 66		SF-36 nonresponders, n = 92		*P* value
	Number (missing)	Value	Number (missing)	Value		Number (missing)	Value	Number (missing)	Value	
Patient demographic information										
Male	28 (0)	55%	34 (0)	49%	.5	34 (0)	52%	53 (0)	58%	.4
DiGeorge syndrome	9 (0)	18%	19 (0)	28%	.2	9 (0)	14%	15 (0)	16%	.6
Other cardiac anomalies	12 (0)	24%	13 (0)	19%	.5	9 (0)	14%	19 (0)	21%	.3
Other medical problems	14 (0)	27%	35 (0)	51%	.01	22 (0)	33%	25 (0)	27%	.4
Patient data at time of questionnaire completion										
Age, y	51 (0)	15.6 ± 1.5, 15.8 (12.9-17.8)	69 (0)	15.7 ± 1.39, 15.9 (13.2-18.0)	.9	66 (0)	19.9 ± 1.3, 19.6 (18.0-23.2)	92 (0)	20.5 ± 1.7, 20.3 (18.0-23.6)	.05
Total medications being taken	51 (0)	1.0 ± 1.3, 0.0 (0.0-5.0)	N/A	N/A	N/A	65 (1)	0.9 ± 1.4, 0.0 (0.0-9.0)	N/A	N/A	N/A
Median neighborhood family income from last census adjusted for inflation (USD)	49 (2)	64,306.2 ± 26,676.0, 58,786.5 (18,143.8-128,666.8)	N/A	N/A	N/A	63 (3)	70,319.2 ± 27,540.0, 64,111.3 (16,633.1-140,766.4)	N/A	N/A	N/A
Patient morphologic information										
Type A IAA	19 (0)	37%	19 (0)	28%	.3	23 (0)	35%	32 (0)	35%	1.0
Type B IAA	31 (0)	61%	50 (0)	72%	.2	43 (0)	65%	60 (0)	65%	1.0
Isolated VSD	38 (0)	75%	55 (0)	80%	.5	54 (0)	82%	68 (0)	74%	.2
Large VSD size	32 (0)	63%	49 (0)	71%	.3	47 (0)	71%	67 (0)	73%	.8
Presence of an anomalous right subclavian	12 (0)	24%	12 (0)	17%	.4	14 (0)	21%	24 (0)	26%	.5
Presence of a bicuspid aortic valve	13 (0)	25%	14 (0)	20%	.5	26 (0)	39%	37 (0)	40%	.9

(Continued)

APPENDIX E2. Continued

Variable	CHQ-CF87, n = 51		CHQ-CF87 nonresponders, n = 69		*P* value	SF-36, n = 66		SF-36 nonresponders, n = 92		*P* value
	Number (missing)	Value	Number (missing)	Value		Number (missing)	Value	Number (missing)	Value	
Characteristics of index repair										
Weight at index IAA repair, kg	40 (11)	3.42 ± 0.94, 3.39 (2.20-8.00)	52 (17)	3.14 ± 0.44, 3.20 (2.20-4.00)	.09	59 (7)	3.35 ± 0.81, 3.20 (2.00-8.00)	79 (13)	3.29 ± 0.90, 3.10 (1.20-7.00)	.3
Thoracotomy	9 (0)	18%	14 (0)	20%	.7	26 (0)	39%	34 (0)	37%	.8
Direct arch repair	30 (0)	59%	49 (0)	71%	.2	39 (0)	59%	53 (0)	58%	.9
Arch repair using patch	19 (0)	37%	17 (0)	25%	.1	12 (0)	18%	25 (0)	27%	.2
Gore-Tex interposition graft	2 (0)	4%	3 (0)	4%	1.0	11 (0)	17%	10 (0)	11%	.3
Arch repair using homograft pulmonary artery	7 (0)	16%	7 (0)	10%	.4	5 (0)	8%	10 (0)	11%	.5
Cardiopulmonary bypass used	42 (0)	82%	55 (0)	80%	.7	42 (0)	64%	60 (0)	65%	.8
Elapsed time on bypass at index repair, min*	29 (22)	81.31 ± 73.05, 70.00 (0.00-227.00)	46 (23)	82.80 ± 73.84, 79.50 (0.00-326.00)	.8	42 (24)	44.69 ± 59.91, 0.00 (0.00-190.00)	55 (37)	52.31 ± 71.71, 0.00 (0.00-306.00)	.8
Total circulatory arrest used	41 (0)	80%	55 (3)	83%	.7	42 (0)	64%	60 (0)	65%	.8
Total circulatory arrest time at index repair, min	35 (16)	36.40 ± 27.84, 46.00 (0.00-104.00)	47 (22)	41.51 ± 28.49, 46.00 (0.00-105.00)	.5	42 (24)	24.57 ± 31.23, 0.00 (0.00-90.00)	63 (29)	25.73 ± 30.08, 0.00 (0.00-109.00)	.7
Procedural sequence and timing										
Total number of surgical procedures	51 (0)	1.98 ± 1.05, 2.00 (1.00-5.00)	69 (0)	1.51 ± 0.72, 1.00 (1.00-4.00)	.01	66 (0)	2.03 ± 1.05, 2.00 (1.00-4.00)	92 (0)	1.79 ± 0.97, 2.00 (1.00-6.00)	.2
Total number of interventional catheter-based procedures	51 (0)	0.27 ± 0.60, 0.00 (0.00-3.00)	69 (0)	0.42 ± 0.79, 0.00 (0.00-3.00)	.4	66 (0)	0.56 ± 1.36, 0.00 (0.00-8.00)	92 (0)	0.40 ± 0.85, 0.00 (0.00-6.00)	1.0
Total number of other procedures	51 (0)	0.49 ± 0.92, 0.00 (0.00-5.00)	69 (0)	0.41 ± 0.93, 0.00 (0.00-5.00)	.4	66 (0)	0.64 ± 1.25, 0.00 (0.00-9.00)	92 (0)	0.58 ± 1.19, 0.00 (0.00-9.00)	.5

(Continued)

APPENDIX E2. Continued

Variable	CHQ-CF87, n = 51		CHQ-CF87 nonresponders, n = 69		*P* value	SF-36, n = 66		SF-36 nonresponders, n = 92		*P* value
	Number (missing)	Value	Number (missing)	Value		Number (missing)	Value	Number (missing)	Value	
Total number of arch procedures	51 (0)	1.45 ± 0.64, 1.00 (1.00-3.00)	69 (0)	1.32 ± 0.65, 1.00 (1.00-4.00)	.1	66 (0)	1.56 ± 1.01, 1.00 (1.00-7.00)	92 (0)	1.46 ± 0.75, 1.00 (1.00-4.00)	.7
Total number of LVOT procedures	51 (0)	0.43 ± 0.85, 0.00 (0.00-3.00)	69 (0)	0.28 ± 0.59, 0.00 (0.00-3.00)	.5	66 (0)	0.50 ± 0.88, 0.00 (0.00-3.00)	92 (0)	0.26 ± 0.66, 0.00 (0.00-4.00)	.06
Time since last procedure, y	51 (0)	12.63 ± 4.18	N/A	N/A	N/A	64 (2)	15.49 ± 5.15	N/A	N/A	N/A
Time since last surgical procedure, y	51 (0)	12.93 ± 4.10	N/A	N/A	N/A	64 (2)	16.27 ± 4.74	N/A	N/A	N/A
Reoperative procedures										
Reoperation with total circulatory arrest	14 (0)	27%	7 (0)	10%	.01	12 (0)	18%	19 (0)	21%	.7
Circulatory arrest at any time	16 (10)	39%	57 (0)	83%	.8	49 (0)	74%	73 (0)	79%	.5
22q11DS variables										
Genetic or DNA testing	27 (8)	63%	N/A	N/A	N/A	24 (8)	41%	N/A	N/A	N/A
Diagnosed with a genetic condition	19 (8)	44%	N/A	N/A	N/A	17 (9)	30%	N/A	N/A	N/A
Difficulties with learning in school	34 (2)	69%	N/A	N/A	N/A	38 (3)	60%	N/A	N/A	N/A
Behavioral problems in school	9 (3)	19%	N/A	N/A	N/A	10 (4)	16%	N/A	N/A	N/A
Mental health counseling by a social worker, psychologist, or psychiatrist	19 (2)	39%	N/A	N/A	N/A	16 (5)	26%	N/A	N/A	N/A
Medication for mental health problems	13 (1)	26%	N/A	N/A	N/A	8 (5)	13%	N/A	N/A	N/A

(Continued)

APPENDIX E2. Continued

Variable	CHQ-CF87, n = 51		CHQ-CF87 nonresponders, n = 69			SF-36, n = 66		SF-36 nonresponders, n = 92		
	Number (missing)	Value	Number (missing)	Value	*P* value	Number (missing)	Value	Number (missing)	Value	*P* value
Diagnosed with anxiety	6 (5)	13%	N/A	N/A	N/A	10 (5)	16%	N/A	N/A	N/A
Diagnosed with depression	1 (3)	2%	N/A	N/A	N/A	6 (5)	10%	N/A	N/A	N/A
Hearing tested and told it wasn't normal	14 (4)	30%	N/A	N/A	N/A	10 (4)	16%	N/A	N/A	N/A
Wear hearing aids	4 (2)	8%	N/A	N/A	N/A	1 (6)	2%	N/A	N/A	N/A
Low calcium levels ever	10 (17)	29%	N/A	N/A	N/A	12 (15)	24%	N/A	N/A	N/A
Ever calcium supplements or medications to correct calcium levels	10 (6)	22%	N/A	N/A	N/A	9 (8)	16%	N/A	N/A	N/A
Ever thyroid problems	3 (9)	7%	N/A	N/A	N/A	4 (10)	7%	N/A	N/A	N/A
Ever speech therapy	36 (1)	72%	N/A	N/A	N/A	30 (5)	49%	N/A	N/A	N/A
Recurrent childhood infections requiring medication or admission to hospital	14 (2)	29%	N/A	N/A	N/A	12 (6)	6%	N/A	N/A	N/A
Ever told by a doctor you have any abnormal facial features	13 (4)	28%	N/A	N/A	N/A	11 (10)	20%	N/A	N/A	N/A
Ever diagnosed with DiGeorge syndrome	16 (10)	39%	N/A	N/A	N/A	14 (10)	25%	N/A	N/A	N/A

Data are presented as numbers (%) or mean ± standard deviation. Note only variables with >5 events and <40% missing data were included in multivariable analysis. *CHQ-CF87*, Child Health Questionnaire-Child Form 87; *SF-36*, Medical Outcomes Study Short Form-36 Health Survey version 2; *N/A*, not available; *USD*, United States dollars; *IAA*, interrupted aortic arch; *VSD*, ventricular septal defect; *LVOT*, left ventricular outflow tract; *22q11DS*, 22q11 deletion syndrome. *The variable "elapsed time on bypass" (minutes) and the corresponding transformations were included in multivariable analysis although it had 43% of data missing for the CHQ-CF87 (SF-36, missing = 36%) (see explanation in "Methods – Statistical Analysis").

APPENDIX E3. 22Q11 DELETION SYNDROME (22q11DS) DEVELOPMENT, VALIDATION, QUESTIONNAIRE, AND RAW RESPONSES, N = 141

Development and Validation

This questionnaire was developed by first determining the features of 22q11DS as reported in the literature, then the development of the questions with a focus on content and wording, organizing the questions in a meaningful order and format, testing, and validation within the Congenital Heart Surgeons' Society (CHSS) Data Center using cognitive debriefing during development to ensure the questions were appropriately comprehended, and finally revision. The questionnaire assessed patients in the following domains for potential self-reported features of 22q11DS: genetic conditions, learning, behavior, mental health, hearing, health issues related to calcium or thyroid problems, and other medical problems (speech related, infections, and abnormal facial features).

Questionnaire and Raw Responses

Genetic Conditions

1. Have you ever had any genetic or DNA testing? Please check one only.

Yes	72 = 52%
No	52 = 38%
Do not know	14 = 10%
Missing	3 = 2%

2. If you have had genetic or DNA testing, why did you have this genetic testing done? Please check one only.

I have not had genetic or DNA testing	36/52 = 85%
Possible problem	48/70 = 69%
Routine Testing	2/70 = 3%
Do not know	5/70 = 7%
Other	15/70 = 21%
Missing	2/72 = 7%
If other (please specify)	15
To confirm genetic defect	2
?DiGeorge	3
?22q11	1
?Velocardiofacial syndrome	1
Voluntary	1
Other	7

3. Have you ever been diagnosed with any genetic conditions? Please check one only.

Yes	48 = 36%
No	77 = 57%
Do not know	10 = 7%
Missing	6 = 4%

4. If the answer to question 3 is yes, with what condition have you been diagnosed?

22q11	8/43 = 19%
DiGeorge	22/43 = 51%
Velocardiofacial syndrome	7/43 = 16%
DiGeorge/velocardiofacial syndrome	1/43 = 2%
Heart-related condition	2/43 = 5%
Truncus arteriosus	1/43 = 2%
Other	2/43 = 5%
Missing	5/48 = 10%

Learning, Behavior, and Mental Health

5. Have you ever had difficulties with learning in school (eg, did you need special assistance)? Please check one only.

Yes	99 = 71%
No	40 = 29%
Do not know	0 = 0%
Missing	2 = 1%

6. If the answer to question 5 is yes, what type of learning problems have you had?

Special education	16/75 = 21%
Subject/language/speech difficulties/cognitive/comprehension/development/processing/learning	45/75 = 60%
Concentration/attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD)	9/75 = 12%
ADHD with either special education or Learning issue	2/75 = 3%
Other	3/75 = 4%
Missing	24/99 = 24%

7. Have you ever had any behavioral problems in school (eg, suspension)? Please check one only.

Yes	27 = 19%
No	111 = 80%
Do not know	1 = 1%
Missing	2 = 1%

8. If the answer to question 7 is yes, what behavioral problems have you had?

Detention/suspension	4/21 = 19%
Anger/frustration/talking back or in class Losing control/hitting/ inappropriate behavior	7/21 = 33%
Social skills	2/21 = 10%
Trouble focusing	1/21 = 5%
Autism/not sitting in seat/not obeying/obsessive-compulsive disorder (OCD)	1/21 = 5%
Apathy	1/21 = 5%
Self-injury/hitting/ threatening/cursing	1/21 = 5%
DiGeorge/anxiety	1/21 = 5%
Panic attacks/autism	1/21 = 5%
ADHD/Graves' disease	1/21 = 5%
Nothing serious	1/21 = 5%
Missing	6/27 = 22%

9. Have you ever had any mental health counseling by a social worker, psychologist, or psychiatrist? Please check one only.

Yes	50 = 36%
No	88 = 63%
Do not know	2 = 1%
Missing	1 = 1%

10. If the answer to question 9 is yes, why did you have counseling?

Mood/fear/anxiety/depression/suicidal	8/33 = 24%
Psychiatric	1/33 = 3%
Family/divorce/abuse	4/33 = 12%
Behavior/anger	4/33 = 12%
Social skills	1/33 = 3%
ADHD	1/33 = 3%
Autism	2/33 = 6%
Combination of social/ADD/ADHD	1/33 = 3%
Combination ADD/depression/social	1/33 = 3%
Combination behavior/agitation/aggression/ OCD	1/33 = 3%
Patient's request	1/33 = 3%
Parent's request	1/33 = 3%
Psychiatric related	2/33 = 6%
Unable to determine patient's given answer	1/33 = 3%
Other	5/33 = 15%
Don't know	1/33 = 3%
Missing	17/50 = 34%

11. Have you ever taken medication for mental health problems? Please check one only.

Yes	29 = 21%
No	110 = 79%
Do not know	0 = 0%
Missing	2 = 1%

12. Have you ever been diagnosed with anxiety? Please check one only.

Yes	20 = 14%
No	115 = 82%
Do not know	5 = 4%
Missing	1 = 1%

13. Have you ever been diagnosed with depression? Please check one only.

Yes	8 = 6%
No	128 = 92%
Do not know	3 = 2%
Missing	2 = 1%

14. Have you ever been diagnosed with schizophrenia? Please check one only.

Yes	2 = 1%
No	134 = 96%
Do not know	3 = 2%
Missing	2 = 1%

Other Medical Problems
Hearing

15. Have you ever had your hearing tested and been told it wasn't normal? Please check one only.

Yes	31 = 22%
No	104 = 75%
Do not know	4 = 3%
Missing	2 = 1%

16. If the answer to question 15 is yes, why was your hearing abnormal?

Anatomical defect	5/17 = 29%
Hearing loss/deafness	7/17 = 41%
Fluid in ears	2/17 = 12%
Fluid in ears/auditory processing disorder	1/17 = 6%
Chronic ear infections	1/17 = 6%
Don't know	1/17 = 6%
Missing	14/31 = 45%

17. Do you wear hearing aids? Please check one only.

Yes	6 = 4%
No	129 = 96%
Missing	6 = 4%

Calcium

18. Have you ever had low calcium levels? Please check one only.

Yes	27 = 20%
No	85 = 61%
Do not know	27 = 19%
Missing	2 = 1%

19. If the answer to question 18 is yes, why did you have low calcium levels?

As infant/child	4/14 = 29%
DiGeorge/?DiGeorge	3/14 = 21%
Hypoparathyroidism	4/14 = 29%
?Genetic	1/14 = 7%
After heart surgery	1/14 = 7%
During pregnancy	1/14 = 7%
Missing	13/27 = 48%

20. Has a doctor ever given you calcium supplements or medication to correct your calcium levels? Please check one only.

Yes	27 = 20%
No	104 = 76%
Do not know	6 = 4%
Missing	4 = 3%

Thyroid

21. Have you ever had any problems with your thyroid? Please check one only.

Yes	12 = 9%
No	112 = 82%
Do not know	13 = 9%
Missing	4 = 3%

22. If the answer to question 21 is yes, what problem did you have?

Hypothyroidism	4/7 = 57%
Thyroid removal	1/7 = 14%
At birth	1/7 = 14%
Underdeveloped at birth	1/7 = 14%
Missing	5/12 = 42%

Other

23. Have you ever had any speech therapy at any time in your life? Please check one only.

Yes	87 = 63%
No	51 = 37%
Do not know	1 = 1%
Missing	2 = 1%

24. If the answer to question 23 is yes, why did you have speech therapy?

Articulation/pronunciation	19/51 = 37%
Delayed speech	6/51 = 12%
Cognitive issues	6/51 = 12%
Anatomical issues	6/51 = 12%
Cleft palate	5/51 = 10%
Any combination of above	6/51 = 12%
Feeding issues	1/51 = 2%
DiGeorge syndrome	1/51 = 2%
Unclear from patient answer	1/51 = 2%
Missing	36/87 = 41%

25. Did you have recurrent childhood infections requiring medication or admission to hospital? Please check one only.

Yes	30 = 22%
No	106 = 77%
Do not know	1 = 1%
Missing	4 = 3%

26. Have you ever been told by a doctor that you have any abnormal facial features? Please check one only.

Yes	32 = 23%
No	99 = 72%
Do not know	6 = 4%
Missing	4 = 3%

Summary of Findings

Of the 141 (51%) patients who completed the 22q11DS questionnaire, 52% (72/141) reported having undergone genetic testing. Of those who had genetic testing, 48 of 70 (69%) had testing to assess for a possible problem, as opposed to routine testing. The percentage of patients who answered the questionnaire who reported having been diagnosed with a genetic condition was

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36% (48/135). Of these, 5 patients did not report their diagnosis. Of the remaining, 8 of 43 (19%) reported a diagnosis of 22q11DS, 22 of 43 (51%) reported DiGeorge, and 7 of 43 (16%) reported velocardiofacial syndrome. The complete set of responses are listed in Appendix E3, question 4. This is in contrast to 20% of patients (28/141) who were noted as having DiGeorge, as recorded in the medical records that were reviewed. Of note, many patients may not have been genetically tested secondary to the lack of testing available in the late 1980s and early 1990s, or may not have been clinically suspected of having the syndrome due to the wide spectrum of disease phenotypes (some cases being very mild). Therefore, in the remainder of the questionnaire we attempted to determine the prevalence of associated features, regardless of a 22q11DS diagnosis, based on self-report using the 22q11DS questionnaire we had developed.

In the second section of the questionnaire, we asked patients about their learning, behavior, and mental health, as patients with 22q11DS often have deficiencies in these areas. We found that 71% (99/140) of patients who responded to the questionnaire reported difficulties with learning in school. Of the 99 who reported difficulties in school, 75 further described their learning problem, with 12% (9/75) reporting issues related to concentration/attention deficit disorder/attention deficit hyperactivity disorder, and 21% (16/75) receiving special education. We also found that 19% (27/139) self-reported behavioral problems, and the reasons varied widely. Finally, 36% (50/140) of respondents reported having had mental health counseling for a wide variety of reasons, including mood/fear/anxiety/depression/suicide (24% = 8/33), family-related issues (12% = 4/33), and behavior/anger issues (12% = 4/33). In addition, 21% (29/140) of patients reported having taken medications for mental health issues, 14% (20/140) had been diagnosed with anxiety, 6% (8/139) with depression, and 1% (2/139) had been diagnosed with schizophrenia (which has a known association with 22q11DS).

In the third section of the questionnaire, we assessed other 22q11DS-associated medical problems. The percentage of patients who reported having had their hearing tested and having abnormal results was 22% (31/139), and 4% of patients (6/135) reported the need to use hearing aids. Another commonly associated feature is hypocalcemia, and 20% (27/139) of patients self-reported this, with the same number reporting having taken calcium supplements or medications to correct their calcium levels. The last 2 questions of this section related to thyroid problems, which were self-reported by 9% (12/137).

In the last section of the questionnaire, we assessed speech therapy, recurrent childhood infections and abnormal facies. Undergoing speech therapy was self-reported by 63% (87/139) of patients, with 37% (19/51) of these patients undergoing speech therapy for articulation and pronunciation. In addition, 22% (30/137) reported recurrent infections requiring medication or admission to hospital. Surprisingly, 23% (32/137) of patients reported having been told they had abnormal facial features by a doctor.

The changing denominator in the above results is due to missing responses.

APPENDIX E4. DETAILED DESCRIPTION OF ADDITIONAL DATA COLLECTION, CONSENT, AND STATISTICAL METHODS

Data Collection

Additional patient data were abstracted from copies of medical records submitted to the CHSS Data Center annually. These included records for initial and subsequent assessments, hospitalizations, and procedures. They were entered into a database by CHSS Data Center staff and member surgeons. These variables have been defined and described in our previous work.[22]

Consent

Institutional and patient participation was voluntary and confidential. Patients provided informed consent. Ethics approval for the CHSS Data Center is obtained annually from the Research Ethics Board of the Hospital for Sick Children, Toronto, Ontario, Canada. Institutional approval was obtained from the local site's institutional review board.

Statistical Methods

Data are expressed as the frequency, median with the range, or mean and standard deviation, with the number of missing values indicated. Response bias was sought by comparing categorical data for responders versus non-responders using the χ^2 or Fisher exact tests and continuous variables using the Wilcoxon 2-sample test. As both the Child Health Questionnaire-Child Form 87 (CHQ-CF87) and Medical Outcomes Study Short Form-36 Health Survey version 2 (SF-36) are measured on different scales, with the CHQ-CF87 scored out of 100 and the SF-36 centered on a score of 50, we derived z scores for our data using the published normative values to look at deviations from normal. This allowed for comparison between adolescents and young adults. For the CHQ-CF87, published scores obtained from 278 healthy children aged 10 to 15 years from a middle school in northeast United States were used as a normative reference.[21] For the SF-36, normative comparison data was taken from the User's Manual for the SF-36v2 Health Survey and matched for age.[20] Functional health status (FHS) scores of patients with interrupted aortic arch were compared with normative data using single-sample *t* tests against a hypothesized mean. Multivariable linear regression was performed to assess associations with

scores on each of the CHQ-CF87 and SF-36 scales with the variables listed in Appendix E2, along with data taken from the 22q11DS questionnaire. To identify the demographic, socioeconomic, lifestyle, morphologic, and procedure-related factors associated with the domains of the FHS questionnaires (ie, Physical Functioning, General Health, etc), a bootstrap bagging algorithm (1000 samples) was used that included all potential variables associated with the outcomes, with the exception of variables with an unacceptable amount of missing data (>40% missing) or <5 events (Appendix E2). Missing data were imputed using the technique of mean imputation. The variable ''elapsed time on bypass'' (minutes) and the corresponding transformations were included in multivariable analysis although it had 43% of data missing for the CHQ-CF87 (SF36, missing = 36%). We elected to include this variable, as it had a borderline amount of missing data only for one questionnaire. Clusters were also created that either solely included mathematical transformation of continuous variables, or in 4 cases had groups of related variables. These groups pertained to ''patient reporting DNA testing'' of any type, grouping use of ''calcium supplements'' and ''medications to correct calcium levels,'' presence of any ''other medical problems,'' and ''having a diagnosis of a genetic condition'' of any kind. Factors selected in at least 50% of the bootstrap samples were selected for further modeling. The final multivariable model for each FHS score was obtained through stepwise multivariable regression modeling, with backward selection of the variables selected using bootstrapping. Of note, final models in which any variables selected had missing data were further assessed to determine whether the missing data was important by using missing variable markers. Correlations were also assessed, and none were found to be present related to variables in the final models. Reliability indicates the percentage of bootstrap samples in which a given factor was selected. All regression models used a maximum likelihood algorithm to determine parameter estimates. All analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute, Inc, Cary, NC).