International Journal of Cardiology Congenital Heart Disease 5 (2021) 100200

Contents lists available at ScienceDirect

International Journal of Cardiology Congenital Heart Disease

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-congenital-heart-disease

Pain in adults with congenital heart disease - An international perspective

Allison Leibold [a], Erin Eichler [a], Sukyung Chung [b], Philip Moons [c,d,e,f], Adrienne H. Kovacs [g,h], Koen Luyckx [i,j], Silke Apers [c], Corina Thomet [k], Werner Budts [l,m], Junko Enomoto [n], Maayke A. Sluman [o,p], Jou-Kou Wang [q], Jamie L. Jackson [r], Paul Khairy [s], Stephen C. Cook [t], Shanthi Chidambarathanu [u], Luis Alday [v], Erwin Oechslin [g], Katrine Eriksen [w], Mikael Dellborg [c,x,y], Malin Berghammer [z,aa], Bengt Johansson [ab], Andrew S. Mackie [ac], Samuel Menahem [ad], Maryanne Caruana [ae], Gruschen Veldtman [af], Alexandra Soufi [ag], Kamila White [ah], Edward Callus [ai,aj], Shelby Kutty [ak,al], Susan M. Fernandes [a,am,an,*], on behalf of the APPROACH-IS consortium, the International Society for Adult Congenital Heart Disease (ISACHD)

[a] *Office of PA Education, Stanford University, School of Medicine, Stanford, CA, USA*
[b] *Quantitative Sciences Unit, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA, USA*
[c] *KU Leuven Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium*
[d] *Institute of Health and Care Sciences, University of Gothenburg, Gothenburg, Sweden*
[e] *Centre for Person-Centered Care (GPCC), University of Gothenburg, Gothenburg, Sweden*
[f] *Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa*
[g] *Toronto Congenital Cardiac Center for Adults, University Health Network, University of Toronto, Toronto, Canada*
[h] *Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA*
[i] *KU Leuven School Psychology and Development in Context, KU Leuven, Leuven, Belgium*
[j] *UNIBS, University of the Free State, Bloemfontein, South Africa*
[k] *Center for Congenital Heart Disease, Department of Cardiology, Inselspital - Bern University Hospital, University of Bern, Bern, Switzerland*
[l] *Division of Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium*
[m] *KU Leuven Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium*
[n] *Department of Education, Toyo University, Tokyo, Japan*
[o] *Coronel Institute of Occupational Health, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*
[p] *Department of Cardiology, Jeroen Bosch Hospital, 's Hertogenbosch, the Netherlands*
[q] *Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan*
[r] *Center for Biobehavioral Health, Nationwide Children's Hospital, Columbus, OH, USA*
[s] *Adult Congenital Heart Center, Montreal Heart Institute, Université de Montréal, Montreal, Canada*
[t] *Indiana University Health Adult Congenital Heart Disease Program, Indianapolis, IN, USA*
[u] *Pediatric Cardiology, Frontier Lifeline Hospital (Dr. K. M. Cherian Heart Foundation), Chennai, India*
[v] *Division of Cardiology, Hospital de Niños, Córdoba, Argentina*
[w] *Adult Congenital Heart Disease Center, Oslo University Hospital - Rikshospitalet, Oslo, Norway*
[x] *Adult Congenital Heart Unit, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden*
[y] *Institute of Medicine, The Sahlgrenska Academy at University of Gothenburg, Sweden*
[z] *Department of Health Sciences, University West, Trollhättan, Sweden*
[aa] *Department of Paediatrics, Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden*
[ab] *Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*
[ac] *Division of Cardiology, Stollery Children's Hospital, University of Alberta, Edmonton, Canada*
[ad] *Monash Heart, Monash Medical Centre, Monash University, Melbourne, Australia*
[ae] *Department of Cardiology, Mater Dei Hospital, Birkirkara Bypass, Malta*
[af] *Adult Congenital Heart Disease Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA*
[ag] *Department of Cardiac Rehabilitation, Médipôle Lyon-Villeurbanne, Lyon, France*
[ah] *Adult Congenital Heart Disease Center, Washington University and Barnes Jewish Heart & Vascular Center, University of Missouri, Saint Louis, MO, USA*
[ai] *Clinical Psychology Service, IRCCS Policlinico San Donato, Milan, Italy*
[aj] *Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy*
[ak] *Adult Congenital Heart Disease Center University of Nebraska Medical Center/ Children's Hospital and Medical Center, Omaha, NE, USA*
[al] *Taussig Heart Center, Johns Hopkins School of Medicine, Baltimore, MD, USA*
[am] *Department of Medicine, Division of Cardiovascular Medicine, Stanford University, School of Medicine, Palo Alto, CA, USA*
[an] *Department of Pediatrics, Division of Pediatric Cardiology, Stanford University, School of Medicine, Palo Alto, CA, USA*

* Corresponding author. Stanford University School of Medicine, Office of PA Education, 1265 Welch Road, Suite 100, Stanford, CA, 94305, USA.
E-mail address: smf14@stanford.edu (S.M. Fernandes).

https://doi.org/10.1016/j.ijcchd.2021.100200
Received 20 April 2021; Received in revised form 22 July 2021; Accepted 24 July 2021

ARTICLE INFO

Keywords:
Adult congenital heart disease
Congenital heart disease
Chronic pain
Patient reported outcomes

ABSTRACT

Background: Patients with adult congenital heart disease (ACHD) have many risk factors for chronic pain such as prior cardiac interventions and adult comorbidities. However, the prevalence of chronic pain has not been well described in this population. We sought to determine the prevalence of pain in a large international cohort of patients with ACHD.

Methods: Data from the APPROACH-IS dataset was utilized for this study which includes 4028 patients with ACHD from 15 different countries. The prevalence of pain was assessed under the health status patient reported outcome domain utilizing the EuroQol-5D 3 level version tool. Multivariable logistic regression was used to assess differences across countries in pain, taking into account country-level random effects for clustering across observations within each country.

Results: A total of 3832 patients with ACHD met the study criteria, median age 32 years [IQR 25, 42], 52.6% females. The prevalence of at least moderate pain was reported by 28.9% (95% CO 27.5 = 30.3%) of participants. Pain was associated with country of origin, age, gender, background, education and marital status as well as several clinical variables including disease complexity, cardiac device presence, history of heart failure, psychiatric conditions and presence of other medical conditions. Those with pain had lower levels of perceived health and a lower quality of life score.

Conclusion: Pain in patients with ACHD is common, impacting nearly one-third of patients. Given the far reaching implications of pain in patients with ACHD, further study of pain characteristics and treatment management appear warranted.

1. Introduction

The opioid epidemic has brought a renewed focus on chronic pain, which is a global problem impacting approximately 20% of the adult population [1–3]. Historically, female gender and increasing age are associated with a higher prevalence of pain [2]. In addition, other factors such as prior surgery [4], unmet surgical needs [1], and underlying chronic disease are contributing factors [5] that patients with Adult congenital heart disease (ACHD) are likely to experience. The majority of these patients have had at least one cardiovascular operation. Many have residual cardiac issues and associated end-organ dysfunction [6]. The prevalence of adult comorbidities is also greater in the ACHD population than the general population [6–12]. In particular, these patients experience a higher prevalence of psychosocial issues, specifically anxiety, depression, and post-traumatic stress disorder [13–15], which likely places them at higher risk for pain. Given this, we sought to describe the prevalence of pain in a large international cohort of patients with ACHD, specifically exploring geographic differences and demographic and clinical characteristics associated with pain.

2. Methods

We conducted a substudy of the "Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease- International Study" (APPROACH-IS) [16]. The APPROACH-IS study enrolled 4028 patients from 15 different countries. These countries include; Argentina (N = 178), Australia (N = 132), Belgium (N = 276), Canada (N = 523), France (N = 96), India (N = 200), Italy (N = 66), Japan (N = 257), Malta (N = 119), Norway (N = 174), Sweden (N = 471), Switzerland (N = 278), Taiwan (N = 250), the Netherlands (N = 256), and the United States (US) of America (N = 752). The inclusion and exclusion criteria have been previously reported in a paper outlining the rationale, design, and methods for the APPROACH IS study [16]. In brief, inclusion criteria were "(1) diagnosis of congenital heart disease (CHD), (2) age $\geq$ 18 years, (3) diagnosis established before adolescence, (4) continued follow-up at CHD center or included in a national or regional registry, and (5) physical, cognitive, and language capabilities to complete self-report questionnaires." Exclusion criteria were; "(1) heart transplantation, and (2) diagnosed idiopathic pulmonary arterial hypertension." [16] Patients who qualified to be part of the APPROACH-IS study received their surveys either in clinic or by mail. For this particular substudy, those who did not have pain ratings via the EQ-5D-3L 27/4028 (1%) were excluded as were those who had reported their most recent cardiac surgery to be the same year as the survey completion 169/4028 (5%). There were no significant demographic differences between those who were excluded from this substudy and those who were not.

APPROACH-IS was developed to describe patient-reported outcomes (PRO) for a large international cohort of patients with ACHD. The PROs covered several domains, including the perception of health status, health behaviors, psychological functioning, and quality of life. Perceived health status was assessed using two measures, the 12-item short form health survey version 2 (SF-12v2) and the EuroQol-5D 3 level version (EQ-5D-3L). Both tools cover a breadth of health dimensions and were utilized for this study. The SF-12 measures physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems, and mental health [17]. The EQ-5D-3L includes five dimensions that are used to describe "health state." The dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; respondents are asked how they would describe their health that day. Response options for pain/discomfort are: "I have no pain or discomfort", "I have moderate pain or discomfort", or "I have extreme pain or discomfort." The EQ-5D-3L tool also includes an analog scale for patients to report overall health state from 0 ("worst health you can imagine)" to 100 ("best imaginable health state") [16,18,19] Health behaviors refer to behaviors that may compromise or enhance health. To measure this, the Health Behavior Scale- Congenital Heart Disease (HBS-CHD) data was collected and utilized for this study. HBS-CHD evaluates alcohol consumption, tobacco use, dental care, and physical activity [20]. Lasty, for this study, the Hospital Anxiety and Depression Scale (HADS) data, was used to assess psychological functioning with higher scores indicating higher psychological distress [21]. In addition, the Linear Analog Scale (LAS) and the Satisfaction With Life Scale (SWLS) data was used to assess quality of life in our study population. LAS is a scale measured by 0–100, from worst imaginable to best imaginable, and SWLS is comprised of five statements with responses ranging from "strongly disagree" to "strongly agree." [22].

Demographic data such as age, background/ethnicity, gender, highest level of education, and marital status were collected from participants via a self-reported questionnaire. The primary investigator and their research team at each participating center provided the clinical data which included type of CHD and complexity [23], number of cardiac surgeries and admissions, the presence of a cardiac device, and a history of heart failure, arrhythmias and other co-morbid conditions.

2.1. Statistical analyses

Patient characteristics were summarized as median and interquartile

Table 1
Characteristics associated with pain in adult with congenital heart disease.

Variable	All N = 3832	Pain N = 1107	No Pain N = 2725	p-value[a]
Demographic				
Age, median (IQR)	32 (25, 42) (n = 3825)	34 (26, 46) (n = 1103)	31 (24, 40) (n = 2722)	<0.001
Female Gender	2008 (52.6%)	650 (59.1%)	1358 (50.0%)	<0.001
Background/Ethnicity				<0.001
Asian	737 (19.2%)	178 (16.1%)	559 (20.5%)	
Black	38 (1.0%)	20 (1.8%)	18 (0.7%)	
Hispanic	125 (3.3%)	51 (4.6%)	74 (2.7%)	
White	2825 (73.7%)	818 (73.9%)	2007 (73.7%)	
Other	29 (0.8%)	8 (0.7%)	21 (0.8%)	
Missing	78 (2.0%)	32 (2.9%)	46 (1.7%)	
Highest level of education				<0.001
Less than high school	212 (5.5%)	96 (8.7%)	116 (4.3%)	
High school	1636 (42.7%)	553 (50.0%)	1083 (39.7%)	
College degree	1949 (50.9%)	447 (40.4%)	1502 (55.1%)	
Missing	35 (0.9%)	11 (1.0%)	24 (0.9%)	
Marital Status				<0.001
Married or living with partner	1942 (50.7%)	565 (51.0%)	1377 (50.5%)	
Never married	1675 (43.7%)	449 (40.6%)	1226 (45.0%)	
Divorced or widowed	191 (5.0%)	82 (7.4%)	109 (4.0%)	
Other	5 (0.1%)	1 (0.1%)	4 (0.1%)	
Missing	19 (0.5%)	10 (0.9%)	9 (0.3%)	
Clinical				
Number of cardiac surgeries, median (IQR)	1 (1, 2) (n = 3623)	1 (1, 3) (n = 1065)	1 (1, 2) (n = 2558)	<0.001
Inpatient cardiac admissions within past year	549 (14.5%)	200 (18.4%)	349 (13.0%)	<0.001
Number of cardiac hospitalizations, median (IQR)	0 (0, 1) (n = 3610)	1 (0, 2) (n = 1044)	0 (0, 1) (n = 2566)	<0.001
Complexity of the cardiac defect				<0.001
Simple	1006 (26.3%)	252 (22.8%)	754 (27.7%)	
Moderate	1833 (47.8%)	520 (47.0%)	1313 (48.2%)	
Great	993 (25.9%)	335 (30.3%)	658 (24.1%)	
Cardiac device				<0.001
None	2977 (77.7%)	823 (74.3%)	2154 (79.0%)	
ICD	112 (2.9%)	45 (4.1%)	67 (2.5%)	
PM	280 (7.3%)	126 (11.4%)	154 (5.7%)	
Missing	463 (12.1%)	113 (10.2%)	350 (12.8%)	
Congestive heart failure				<0.001
Never	3361 (87.7%)	914 (82.6%)	2447 (89.8%)	
Past, not current	278 (7.3%)	102 (9.2%)	176 (6.5%)	
Current	128 (3.3%)	73 (6.6%)	55 (2.0%)	
Missing	65 (1.7%)	18 (1.6%)	47 (1.7%)	
History of arrhythmia	1034 (27.2%)	394 (35.9%)	640 (23.6%)	<0.001
Other medical condition	1651 (43.4%)	575 (52.4%)	1076 (39.7%)	<0.001
Psychiatric conditions	391 (10.2%)	197 (17.9%)	194 (7.1%)	<0.001
Mood disorder (ever)	242 (6.4%)	136 (12.4%)	106 (3.9%)	<0.001
Anxiety disorder (ever)	181 (4.7%)	97 (8.8%)	84 (3.1%)	<0.001
Other psychiatric diagnosis (ever)	69 (1.8%)	28 (2.5%)	41 (1.5%)	0.030

[a] Wilcoxon rank-sum test was used for continuous variables and Pearson's chi-square test was used for categorical variables.

range (IQR) for continuous variables and frequency and proportion for categorical variables. Unadjusted differences in the demographic and clinical characteristics between those who did and did not report pain were compared. In statistical testing, the Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables were used. Multivariable logistic regression was used to assess differences in pain across countries, adjusting for patient demographic and clinical characteristics that were considered as potential confounders. Country-level random effects models were used to take into account clustering across observations within each country. A two-sided *p*-value <0.05 was considered to indicate statistical significance. All analyses were performed using Stata 16.0 (College Station, TX, US).

The APPROACH-IS study was coordinated at the University Hospitals Leuven/KU Leuven, Belgium and is compliant with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov: NCT02150603. The Stanford University, Institutional Review Board approved this study, as well as the local institutional review boards at each participating center.

3. Results

3.1. Demographic and clinical characteristics

A total of 3832 patients met our inclusion criteria. The demographic and clinical characteristics of the study participants are summarized in Table 1. The median age was 32 years [IQR 25, 42], and slightly more than half (52.6%) were female. The majority of participants were White (73.7%), and half had a college degree (50.9%). The complexity of CHD was simple for 26.3%, moderate for 47.8%, and great for 25.9%. A substantial proportion of participants (80.2%) had at least one prior cardiovascular operation. A cardiac implantable electronic device was reported by 10.2% of participants (7.3% permanent pacemaker and 2.9% implantable cardioverter-defibrillator). A history of heart failure and arrhythmias were noted by 10.6% and 27.2% of participants respectively. The most common co-morbid conditions reported by the participants were systemic hypertension (6.5%), reactive airway disease (2.5%), dyslipidemia (1.5%), and diabetes (1.4%).

3.2. Prevalence of pain

At the time of the survey completion, 28.9% [95% CI 27.5%–30.3%]

Table 2
Pain in adult with congenital heart disease by country.

Variable	All N = 3832	Pain N = 1107	No Pain N = 2725	p-value[a]
Country				<0.001
Argentina	169 (4.4%)	47 (4.2%)	122 (4.5%)	
Australia	124 (3.2%)	30 (2.7%)	94 (3.4%)	
Belgium	268 (7.0%)	84 (7.6%)	184 (6.8%)	
Canada	493 (12.9%)	178 (16.1%)	315 (11.6%)	
France	85 (2.2%)	29 (2.6%)	56 (2.1%)	
India	189 (4.9%)	67 (6.1%)	122 (4.5%)	
Italy	58 (1.5%)	16 (1.4%)	42 (1.5%)	
Japan	241 (6.3%)	47 (4.2%)	194 (7.1%)	
Malta	113 (2.9%)	24 (2.2%)	89 (3.3%)	
Norway	169 (4.4%)	58 (5.2%)	111 (4.1%)	
Sweden	465 (12.1%)	118 (10.7%)	347 (12.7%)	
Switzerland	269 (7.0%)	83 (7.5%)	186 (6.8%)	
Taiwan	239 (6.2%)	45 (4.1%)	194 (7.1%)	
The Netherlands	239 (6.2%)	62 (5.6%)	177 (6.5%)	
USA	711 (18.6%)	219 (19.8%)	492 (18.1%)	

[a] Derived from Pearson's Chi-square test.

of patients described having at least moderate pain (27.2% moderate and 1.7% extreme pain). The prevalence of pain increased with age and was 23.9% (95% CI 21.8%–25.9%) for those 18–29 years of age, 29.2% [95% CI 26.8%–31.6%] for those 30–44 years of age, 36.5% (95% CI 32.9%–40.2%) for patients 45–64 years of age and for those over 65 years of age, 47.0% (95% CI 38.3%–55.6%) reported pain ($p < 0.001$). Among the 15 different countries included in APPROACH IS, Canada, India, Norway, and had the highest proportion of participants reporting pain (36.1%, 35.4%, 34.3%, and 34.31%, respectively, see Table 2). The prevalence of pain was lowest in Japan (19.5%), followed by Taiwan (18.8%).

3.3. Factors associated with pain

Demographic and clinical variables associated with pain in univariable analyses are provided in Table 1. Female patients were more likely to report pain than male patients (59.1% *versus* 40.9%, $p < 0.001$), as were those with less than a college degree (40.4% *versus* 55.1%, $p < 0.001$). Those who reported pain were also older (34 years [IQR 26, 46] *versus* 31 years [IQR 24, 40], $p < 0.001$). Clinical variables that were associated with pain included disease complexity, co-morbidities, and cardiac interventions. Those who had at least one cardiac surgery were more likely to experience pain than those without a prior cardiac surgery (30.3% *versus* 25.6%, respectively, $p = 0.012$). Those with CHD of great complexity were more likely to describe having pain than those with less complex disease (33.7% *versus* 27.2% respectively, $p < 0.001$). The prevalence of pain by CHD diagnosis are provided in Table 3. The diagnoses associated with the highest prevalence of pain were cyanotic CHD or Eisenmenger physiology (52.8%, 95% CI 41.0%–64.6%), conduits (41.7%, 95% CI 28.8%–54.5%), and tricuspid atresia (41.0%, 95% CI 24.9%–57.2%).

A logistic regression with "country" random effects was employed to identify independent predictors associated with pain (Table 4). After controlling for potential confounders, participants from India, Canada, Norway, Belgium, Italy, Australia and France were more likely to report pain, while those from Argentina were less likely to report pain. Those patients with ACHD who were older (OR 1.02, 95% CI 1.02–1.03, $p < 0.001$), female (1.55, 95% CI 1.32–1.82, $p < 0.001$), Black (2.52, 95% CI 1.62–3.93, $p < 0.001$), Hispanic (OR 2.56, 95% CI 2.00–3.27, $p < 0.001$), had lower educational attainment level (OR 0.56, 95% CI 0.43–0.73, $p < 0.001$), or who were not married (OR 0.83, 95% Ci 0.72–0.96, $p = 0.011$), had an increased odds of reporting pain. Lastly, the clinical variables identified as being independent predictors of pain included disease complexity (OR 1.14, 95% CI 1.01–1.29, $p = 0.037$), cardiac device presence (OR 1.40, 95% CI 1.16–1.69, $p < 0.001$), heart failure (OR 1.91, 95% CI 1.36–2.67, $p < 0.001$), and psychiatric (OR 2.36, 95% CI 1.99–2.80, $p < 0.001$) and other medical conditions (OR 1.36, 95% CI 1.14–1.61, $p < 0.001$).

3.4. Association between pain and other patient-reported outcomes

The patients with ACHD who reported pain were more likely to report

Table 3
Presence of pain by congenital heart disease diagnosis.

Variable		All N = 3832	Pain N = 1107
Congenital heart disease diagnosis		**N**	**%, (95% Confidence Intervals)**
Isolated aortic valve disease	269		22.7%, (17.6%–27.7%)
Small atrial or ventricular septal defect	255		22.4%, (17.2%–27.5%)
Small patent ductus arteriosus	13		15.4%[a]
Repaired atrial or ventricular septal defect or patent ductus arteriosus	361		27.7%, (23.1%–32.3%)
Other defect of simple complexity	108		28.7%, (20.0%–37.4%)
Fistula (aorto-left ventricular/sinus of valsalva)	4		25.0%[a]
Anomalous pulmonary venous drainage or sinus venosus atrial septal defect	59		35.6%, (23.0%–48.2%)
Atrioventricular septal defects or primum atrial septal defect	98		25.5%, (16.7%–34.3%)
Coarctation of the aorta	384		26.3%, (21.9%–30.7%)
Ebstein anomaly	88		31.8%, (21.9%–41.7%)
Infundibular right ventricular outflow tract obstruction of significance	6		33.3%[a]
Pulmonary valve disease with stenosis or regurgitation	220		30.0%, (23.9%–36.1%)
Subvalvar or supravalvar aortic stenosis	143		26.6%, (19.3%–33.9%)
Repaired tetralogy of Fallot	582		27.8%, (17.4%–37.9%)
Ventricular septal defect with other complications	76		27.6%, (17.4%–37.9%)
Other defect of moderate complexity	165		33.9%, (26.6%–41.2%)
Conduits (valve or non-valved)	60		41.7%, (28.8%–54.5%)
Cyanotic heart disease or Eisenmenger syndrome	72		52.8%, (41.0%–64.6%)
Double outlet ventricle	74		29.7%, (19.1%–40.4%)
Univentricular anatomy (Fontan circulation)	170		34.7%, (27.5%–41.9%)
Pulmonary atresia (all forms)	92		35.9%, (25.9%–45.9%)
Repaired transposition of the great arteries	343		30.6%, (25.7%–35.5%)
Congenitally corrected transposition of the great arteries	68		23.5%, (13.2%–33.9%)
Tricuspid atresia	39		41.0%, (24.9%–57.2%)
Truncus arteriosus	20		30.0%, (8.0%–52.0%)
Other defect of great complexity	63		23.8%, (13.0%–34.6%)

[a] Too few patients to compute a reliable confidence interval.

Table 4
Characteristics Associated with Pain in Adult with Congenital Heart Disease Logistic regression model adjusting for country-level clustering N = 3766.

Characteristic	Multivariate OR	95% CI lower limit	95% CI upper limit	P-value
Participating Country [ref = USA]				
Argentina	0.834	0.715	0.973	0.021
Australia	1.305	1.116	1.526	0.001
Belgium	1.553	1.332	1.811	<0.001
Canada	1.693	1.596	1.797	<0.001
France	1.289	1.199	1.386	<0.001
India	2.510	1.656	3.805	<0.001
Italy	1.315	1.016	1.703	0.037
Japan	0.691	0.436	1.096	0.117
Malta	0.875	0.738	1.039	0.128
Norway	1.661	1.503	1.837	<0.001
Sweden	1.029	0.930	1.138	0.581
Switzerland	1.280	1.158	1.416	<0.001
Taiwan	0.831	0.530	1.303	0.420
The Netherlands	0.972	0.835	1.132	0.717
Demographic				
Age	1.023	1.016	1.030	<0.001
Sex	1.549	1.317	1.822	<0.001
Background/Ethnicity [ref = White]				
Asian	1.094	0.682	1.753	0.709
Black	2.520	1.615	3.934	<0.001
Hispanic	2.555	1.997	3.270	<0.001
Other	1.312	0.822	2.095	0.255
College degree	0.557	0.426	0.728	<0.001
Married	0.828	0.716	0.958	0.011
Clinical				
Cardiac defect, great complexity	1.141	1.008	1.291	0.037
Cardiac device, any	1.400	1.159	1.690	<0.001
History of arrhythmia	1.223	0.927	1.615	0.155
Current heart failure	1.907	1.361	2.671	<0.001
Other medical condition	1.355	1.143	1.607	<0.001
Psychiatric condition	2.364	1.995	2.802	<0.001

limits to moderate activities such as bowling and golf (52.8% versus 14.3%, $p < 0.001$) and normal work activities (78.2% *versus* 16.2%, $p < 0.001$) than those without pain. Those with pain were also more likely to report difficulty climbing stairs than those without pain (74.8% *versus* 35.3%, $p < 0.001$).

The majority (83.5%) of patients with ACHD in this study considered their health to be at least good, with 11.4% stating their health was excellent and 36.6% very good. Those who reported pain were less likely to report excellent or very good health compared to those without pain (18.7% *versus* 59.4%, $p < 0.001$). In addition, the median quality of life score for those with data on pain was 80.0 [IQR: 70, 90]. Those with pain had a lower quality of life score compared to those without pain (70 [IQR: 60, 80] *versus* 85 [IQR: 75, 90], $p < 0.001$) and were more likely to have a quality of life score below 50 (11.6% *versus* 2.1%, $p < 0.001$).

Alcohol was the most common substance used by patients with ACHD in this study, with 72.7% of participants reporting alcohol use at least once per month with 20.0% using alcohol at least twice per week. Those who reported pain appeared to be less likely to consume alcohol than those without pain (66.8% versus 75.1%, $p < 0.001$). Tobacco use was reported by 12.0% of participant, and sedatives were used by 5.0%. Only 1.1% of participants reported using drugs such as ecstasy, cocaine, hallucinogens, or speed. Tobacco and sedative use were more common in those with pain than those without (14.8% versus 10.9%, $p < 0.001$, and 10.7% versus 3.0%, $p < 0.001$, respectively).

4. Discussion

In this large international cohort of patients with ACHD, nearly one-third experienced at least moderate pain. This pain was associated with limitations to physical activities and work inside and outside the home, as well as lower perceptions of health and quality of life. Geographic variation was observed among the 15 countries included in this study, with the prevalence of pain being highest in India, Canada, Norway, Belgium, Italy, Australia and France after controlling for potential confounders. Argentina had the lowest reported prevalence of pain. In comparison to similar age strata in the general population, the overall prevalence of pain in patients with ACHD appears higher. A meta-analysis reported a 10–15% prevalence of chronic pain in the general population across Asia, Australasia, Middle East, South America, North America, Europe, Scandinavia, and Russia. Consistent with our findings, the authors reported a higher prevalence of pain in the population from Canada and Norway (14.5% and 17.4%, respectively) [24]. Of the 750 participants in the current study from the US, 32.5% reported having pain. This is significantly higher than the 20.4% previously reported in the US general population, which is predominantly driven by those over the age of 65 years [3].

While patients with ACHD appear to have a higher prevalence of pain than the general population, the associations between pain and demographic and clinical variables align with prior literature. Age is a driving factor for pain in the general population, with the prevalence of pain increasing with age [25]. The association between age and pain is complex given the interrelationship between age and co-morbidities and length of time for exposure to injury and toxins [5]. An increase in the prevalence of pain with advancing age was also seen in our patients with ACHD.

The differences in pain by gender, educational attainment, marital status, and ethnicity reported in our study are consistent with prior literature in the general population [3,25,26]. However, there are some conflicting data on the association between pain and ethnicity in prior studies. We found that Black and Hispanic individuals were more likely to report pain. However, previous reports suggested that socioeconomic status, which was not explored in this study, appears to have a more significant influence on pain perception [5]. In addition, those who are socioeconomically deprived reported higher levels of pain and disability [26].

Persistent pain after cardiac surgery may play a role in the prevalence of pain noted in our study. Prior studies have shown that persistent postoperative pain after cardiac surgery is common, with approximately one-third of patients reporting pain 3-months post-surgery and 17% reporting pain at two years. The location of the pain was predominately the chest [27]. Chronic post-procedural pain after cardiac device placement (i.e., permanent pacemaker or defibrillator) has also been reported, with one study suggesting that nearly a quarter of patients reported pain at five-year follow-up [28]. Location of pain was not collected in the APPROACH-IS study, rendering comparisons impossible. Although APPROACH-IS was not designed to determine the cause of chronic pain, it provides a foundation for further exploration of the relationship between cardiac interventions and chronic pain in patients with ACHD.

An association between adult co-morbidities and pain has consistently been reported. In particular, there is a strong association between chronic pain and mental health issues [3,5,26]. Given this, it is not surprising that we found a correlation between co-morbidities and pain in our ACHD patient population. As the literature evolves, it is becoming increasingly clear that patients with ACHD are at greater risk for adult co-morbidities than the general population and, therefore, are presumed to be at greater risk for chronic pain [8,9,11,29–31]. Depression, anxiety, and post-traumatic stress disorder are also common in patients with ACHD [13,14,32]. It remains unclear to what degree pain influences mental health status and vice versa in patients with ACHD. Notwithstanding, psychological interventions may reduce pain perception and in turn improve quality of life. As described in the general population, the interaction between pain and depression appears complex, with one condition impacting the other with many similarities both clinically and biologically [33]. It appears reasonable, therefore, to assess for pain in patients with ACHD and co-morbidities, in particular mental health

conditions. In addition, it should be noted that some patients with ACHD consider themselves to be asymptomatic even when identifying as having pain [34].

Pain in patients with ACHD appears to have associations that impact engagement in physical activities, perceived health, and quality of life. Physical limitations due to the presence of pain are common [35]. In our study, more than three-quarters of those who reported pain had limits to moderate activities (i.e., bowling and household chores) and climbing stairs. Of interest, only 30% of the ACHD population meets World Health Organization activity health recommendations [36]. While the lack of physical activity in patients with ACHD is likely multifactorial; pain may contribute to inactivity in some patients. There also appears to be an association between physical activity and perceived health [37]. While nearly half of the patients with ACHD considered their health to be very good or excellent, those with pain were far less likely to report this level of perceived health. With limits to physical activity and lower perceived health in patients with ACHD who have pain, it is not surprising that quality of life scores were lower. Although quality of life is generally good for patients with ACHD [38], pain may be a contributing factor in some patients with a decreased quality of life. As we consider initiatives to improve the lives of patients with ACHD, our study calls attention to the importance of addressing pain. It remains to be demonstrated whether outcomes can be improved by widespread screening for pain, followed by appropriate referral and management. There is a need to better understand triggers for chronic pain in patients with ACHD and to develop targeted preventative strategies.

The large sample size of the APPROACH-IS study with international representation is a significant strength of this study. However, the results may not be generalizable to the greater ACHD population given that patients enrolled in this study had continued follow-up at a ACHD center or were included in a national or regional registry were included in APPROACH IS. In addition, the population was predominately White, and highly educated. Additional limitations include the cross-sectional nature of the study that precludes causal inferences. Results may have been impacted by social desirability, and recall bias. The variability in recruitment approach, likely resulted in some degree of selection bias. The varying length of time actively recruiting at each site may have impacted the enrollment numbers in each participating country, although attempts were made to control for this in the analyses. In addition, cultural differences may have affected the way participants experience and report pain. Pain was measured differently between our study and various references; therefore, direct comparisons should take variability in measurement of pain into consideration. While recent cardiac surgical interventions were excluded, other procedures that might be associated with post procedural pain could not be excluded as the study was limited by the availability of collected data. Although APPROACH-IS was well suited to assess the prevalence of pain, geographic variabilities, and associations with other patient-reported outcomes, the available data did not permit an in-depth exploration of pain location, timing, frequency, and pharmaceutical and non-pharmaceutical treatments of pain.

In conclusion, in the largest study of pain in patients with ACHD, nearly one-third reported pain, which appears more common than prior reports in an age-stratified general population. Given the relatively young age of the ACHD population and the association between older age and pain, it is likely that the proportion of patients with ACHD and pain will increase over time. Pain appears to impact physical activity, work, perceived health, and quality of life. Pain may also play a role in triggering or exacerbating mental health conditions. Further research is required to elucidate triggers for pain and to assess the impact of preventive and therapeutic interventions.

Disclosures

None.

Funding sources

This work was supported Stanford University Cardiovascular Institute to A.L.; by the Research Fund – KU Leuven (Leuven, Belgium) through grant OT/11/033 to K.L. and P.M.; by the Swedish Heart-Lung Foundation (Sweden) through grant number 20130607 to M.D.; by the University of Gothenburg Centre for Person-centred Care (Gothenburg, Sweden) to M.D. and P.M.; and by the Cardiac Children's Foundation (Taiwan) through grant CCF2013_02 to H.L.Y. Furthermore, this work was endorsed by and conducted in collaboration with the International Society for Adult Congenital Heart Disease.

Collaborators

APPROACH-IS consortium: Luis Alday, Héctor Maisuls, Betina Vega (Córdoba, Argentina, Hospital de Niños); Samuel Menahem, Sarah Eaton, Qi Feng Wang, Ruth Larion (Melbourne, Australia, Monash Medical Center); Werner Budts, Kristien Van Deyk (Leuven, Belgium, University Hospitals of Leuven); Silke Apers, Eva Goossens, Jessica Rassart, Koen Luyckx, Philip Moons (Leuven, Belgium, University of Leuven); Gwen Rempel, Andrew Mackie, Ross Ballantyne, Kathryn Rankin, Colleen Norris, Dylan Taylor, Isabelle Vondermuhll, Jonathan Windram, Pamela Heggie, Gerri Lasiuk (Edmonton, Canada, University of Alberta); Paul Khairy, Anna Proietti, Annie Dore, Lise-Andrée Mercier, François-Pierre Mongeon, François Marcotte, Reda Ibrahim, Blandine Mondésert, Marie-Claude Côté (Montreal, Canada, Montreal Heart Institute); Adrienne Kovacs, Erwin Oechslin, Mimi Bandyopadhyay (Toronto, Canada, University Health Network); Alexandra Soufi, Sylvie Di Filippo, François Sassolas, André Bozio, Cécile Chareyras (Lyon, France, Louis Pradel Hospital); Shanthi Chidambarathanu, Farida Farzana, Nitya Lakshmi (Chennai, India, Frontier Lifeline Hospital, Dr. K. M. Cherian Heart Foundation); Edward Callus, Emilia Quadri, Massimo Chessa, Giovanna Campioni, Alessandro Giamberti (Milan, Italy, IRCCS Policlinco San Donato Hospital); Junko Enomoto, Yoshiko Mizuno (Chiba, Japan, Chiba Cardiovascular Center); Maryanne Caruana, Victor Grech, Sheena Vella, Anabel Mifsud, Neville Borg, Daniel Chircop, Matthew Mercieca Balbi, Rachel Vella Critien, James Farrugia, Yanika Gatt, Darlene Muscat (Msida, Malta, Mater Dei Hospital); Katrine Eriksen, Mette-Elise Estensen (Oslo, Norway, Oslo University Hospital); Mikael Dellborg, Malin Berghammer (Gothenburg, Sweden, Sahlgrenska University Hospital); Eva Mattsson, Anita Strandberg, Pia Karlström-Hallberg (Stockholm, Sweden, Karolinska University Hospital); Bengt Johansson, Anna-Karin Kronhamn (Umeå, Sweden, Umeå University Hospital); Markus Schwerzman, Corina Thomet, Margrit Huber (Bern, Switzerland, University Hospital Bern); Jou-Kou Wang, Chun-Wei Lu, Hsiao-Ling Yang, Yu Chuan Hua (Taipei, Taiwan, National Taiwan University Hospital); Barbara Mulder, Maayke Sluman (Amsterdam, the Netherlands, Amsterdam Medical Center); Marco Post (Nieuwegein, the Netherlands, St. Antonius Hospital); Els Pieper (Groningen, the Netherlands, University Medical Center Groningen); Kathinka Peels (Eindhoven, the Netherlands, Catharina Hospital); Marc Waskowsky (Zwolle, the Netherlands, Isala Clinic); Gruschen Veldtman, Michelle Faust, Colin Lozier, Christy Reed, Jamie Hilfer (Cincinnati, USA, Cincinnati Children's Hospital Medical Center); Curt Daniels, Jamie Jackson (Columbus, USA, Nationwide Children's Hospital); Shelby Kutty, Carolyn Chamberlain, Sara Warta (Omaha, USA, Children's Hospital & Medical Center); Stephen Cook, Morgan Hindes (Pittsburgh, USA, Children's Hospital of Pittsburgh of UPMC); Ari Cedars, Kamila White (Saint Louis, USA, Washington University and Barnes Jewish Heart & Vascular Center, University of Missouri); Susan Fernandes, Anitra Romfh, Kirstie MacMillen (Palo Alto, USA, Stanford University).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Acknowledgements

We wish to thank the APPROACH-IS participants who made this study possible. In addition, we would like to thank all individuals at the participating centers who made substantial contributions to APPROACH-IS.

References

[1] Jackson T, Thomas S, Stabile V, Han X, Shotwell M, McQueen K. Prevalence of chronic pain in low-income and middle-income countries: a systematic review and meta-analysis. Lancet 2015;385(Suppl 2):S10.
[2] Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016;6:e010364.
[3] Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–6.
[4] Gjeilo KH, Stenseth R, Wahba A, Lydersen S, Klepstad P. Chronic postsurgical pain in patients 5 years after cardiac surgery: a prospective cohort study. Eur J Pain 2017;21:425–33.
[5] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123:e273–83.
[6] Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing MG, Gewitz M, Ginns J, Kay JD, Kim YY, Kovacs AH, Krieger EV, Wu FM, Yoo SJ. Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific statement from the American heart association. Circulation 2017;136:e348–92.
[7] Ohuchi H, Miyamoto Y, Yamamoto M, Ishihara H, Takata H, Miyazaki A, Yamada O, Yagihara T. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. Am Heart J 2009;158:30–9.
[8] Deen JF, Krieger EV, Slee AE, Arslan A, Arterburn D, Stout KK, Portman MA. Metabolic syndrome in adults with congenital heart disease. J Am Heart Assoc 2016;5.
[9] Gurvitz M, Ionescu-Ittu R, Guo L, Eisenberg MJ, Abrahamowicz M, Pilote L, Marelli AJ. Prevalence of cancer in adults with congenital heart disease compared with the general population. Am J Cardiol 2016;118:1742–50.
[10] Greutmann M, Tobler D, Kovacs AH, Greutmann-Yantiri M, Haile SR, Held L, Ivanov J, Williams WG, Oechslin EN, Silversides CK, Colman JM. Increasing mortality burden among adults with complex congenital heart disease. Congenit Heart Dis 2015;10:117–27.
[11] Lui GK, Fernandes S, McElhinney DB. Management of cardiovascular risk factors in adults with congenital heart disease. J Am Heart Assoc 2014;3.
[12] Björk A, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital heart defect - a nationwide cohort study. Int J Cardiol 2020;310:58–63.
[13] Jackson JL, Leslie CE, Hondorp SN. Depressive and anxiety symptoms in adult congenital heart disease: prevalence, health impact and treatment. Prog Cardiovasc Dis 2018;61:294–9.
[14] Deng LX, Khan AM, Drajpuch D, Fuller S, Ludmir J, Mascio CE, Partington SL, Qadeer A, Tobin L, Kovacs AH, Kim YY. Prevalence and correlates of post-traumatic stress disorder in adults with congenital heart disease. Am J Cardiol 2016;117:853–7.
[15] Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, Ong L, Colman J, Oechslin E, Nolan RP. Depression and anxiety in adult congenital heart disease: predictors and prevalence. Int J Cardiol 2009;137:158–64.
[16] Apers S, Kovacs AH, Luyckx K, Alday L, Berghammer M, Budts W, Callus E, Caruana M, Chidambarathanu S, Cook SC, Dellborg M, Enomoto J, Eriksen K, Fernandes SM, Jackson JL, Johansson B, Khairy P, Kutty S, Menahem S, Rempel G, Sluman MA, Soufi A, Thomet C, Veldtman G, Wang JK, White K, Moons P. Assessment of Patterns of patient-reported outcomes in adults with congenital heart disease - international study (APPROACH-IS): rationale, design, and methods. Int J Cardiol 2015;179:334–42.
[17] Ware JE, Kosinski M, Tuner-Bowker DM, Sundaram M, Gandek B, Maruish ME. User's manual for the SF-12v2 health survey. second ed. Lincoln, RI: QualityMetric, Incorporated; 2009.
[18] Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. Health Qual Life Outcome 2010;8:13.
[19] EuroQol–a new facility for the measurement of health-related quality of life. Health Pol 1990;16:199–208.
[20] Goossens E, Luyckx K, Mommen N, Gewillig M, Budts W, Zupancic N, Moons P. Health risk behaviors in adolescents and emerging adults with congenital heart disease: psychometric properties of the Health Behavior Scale-Congenital Heart Disease. Eur J Cardiovasc Nurs 2013;12:544–57.
[21] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[22] Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. J Pers Assess 1985;49:71–5.
[23] Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham Jr TP, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol 2008;52:e143–263.
[24] Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain 2016;157:55–64.
[25] Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic pain and high-impact chronic pain among U.S. Adults, 2019. NCHS Data Brief 2020:1-8.
[26] Kim HJ, Yang GS, Greenspan JD, Downton KD, Griffith KA, Renn CL, Johantgen M, Dorsey SG. Racial and ethnic differences in experimental pain sensitivity: systematic review and meta-analysis. Pain 2017;158:194–211.
[27] Guimarães-Pereira L, Reis P, Abelha F, Azevedo LF, Castro-Lopes JM. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. Pain 2017;158:1869–85.
[28] Lewis K, Dai M, Patton KK, Cha YM, Pollema T, Feld GK, Birgersdotter-Green U, Pretorius V. Lead extraction for reduction of chronic pain related to cardiovascular implantable electronic device. Europace 2019;21:781–6.
[29] Cohen S, Gurvitz MZ, Beauséjour-Ladouceur V, Lawler PR, Therrien J, Marelli AJ. Cancer risk in congenital heart disease-what is the evidence? Can J Cardiol 2019;35:1750–61.
[30] Lui GK, Rogers IS, Ding VY, Hedlin HK, MacMillen K, Maron DJ, Sillman C, Romfh A, Dade TC, Haeffele C, Grady SR, McElhinney DB, Murphy DJ, Fernandes SM. Risk estimates for atherosclerotic cardiovascular disease in adults with congenital heart disease. Am J Cardiol 2017;119:112–8.
[31] Mandalenakis Z, Karazisi C, Skoglund K, Rosengren A, Lappas G, Eriksson P, Dellborg M. Risk of cancer among children and young adults with congenital heart disease compared with healthy controls. JAMA Netw Open 2019;2:e196762.
[32] Gleason LP, Deng LX, Khan AM, Drajpuch D, Fuller S, Ludmir J, Mascio CE, Partington SL, Tobin L, Kim YY, Kovacs AH. Psychological distress in adults with congenital heart disease: focus beyond depression. Cardiol Young 2019;29:185–9.
[33] Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–45.
[34] Berghammer M, Karlsson J, Ekman I, Eriksson P, Dellborg M. Self-reported health status (EQ-5D) in adults with congenital heart disease. Int J Cardiol 2013;165:537–43.
[35] Björnsdóttir SV, Jónsson SH, Valdimarsdóttir UA. Functional limitations and physical symptoms of individuals with chronic pain. Scand J Rheumatol 2013;42:59–70.
[36] Larsson L, Johansson B, Sandberg C, Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, Sluman MA, Wang JK, Jackson JL, Khairy P, Cook SC, Alday L, Eriksen K, Dellborg M, Berghammer M, Rempel G, Menahem S, Caruana M, Tomlin M, Soufi A, Fernandes SM, White K, Callus E, Kutty S, Moons P. Geographical variation and predictors of physical activity level in adults with congenital heart disease. Int J Cardiol Heart Vasc 2019;22:20–5.
[37] Ko JM, White KS, Kovacs AH, Tecson KM, Apers S, Luyckx K, Thomet C, Budts W, Enomoto J, Sluman MA, Wang JK, Jackson JL, Khairy P, Cook SC, Subramanyan R, Alday L, Eriksen K, Dellborg M, Berghammer M, Johansson B, Mackie AS, Menahem S, Caruana M, Veldtman G, Soufi A, Fernandes SM, Callus E, Kutty S, Gandhi A, Moons P, Cedars AM. Physical activity-related drivers of perceived health status in adults with congenital heart disease. Am J Cardiol 2018;122:1437–42.
[38] Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, Sluman MA, Wang JK, Jackson JL, Khairy P, Cook SC, Chidambarathanu S, Alday L, Eriksen K, Dellborg M, Berghammer M, Mattsson E, Mackie AS, Menahem S, Caruana M, Veldtman G, Soufi A, Romfh AW, White K, Callus E, Kutty S, Fieuws S, Moons P. Quality of life of adults with congenital heart disease in 15 countries: evaluating country-specific characteristics. J Am Coll Cardiol 2016;67:2237–45.