Canadian Journal of Cardiology 37 (2021) 215–223

Clinical Research

Physical Functioning, Mental Health, and Quality of Life in Different Congenital Heart Defects: Comparative Analysis in 3538 Patients From 15 Countries

Philip Moons, PhD,[a,b,c,d] Koen Luyckx, PhD,[e,f] Corina Thomet, MSc,[a,g] Werner Budts, MD, PhD,[h,i] Junko Enomoto, PhD,[j] Maayke A. Sluman, MD, PhD,[k,l] Chun-Wei Lu, MD, PhD,[m] Jamie L. Jackson, PhD,[n] Paul Khairy, MD, PhD,[o] Stephen C. Cook, MD,[p] Shanthi Chidambarathanu, FNB,[q] Luis Alday, MD,[r] Katrine Eriksen, MSc,[s] Mikael Dellborg, MD, PhD,[c,t,u] Malin Berghammer, PhD,[c,v,w] Bengt Johansson, MD, PhD,[x] Andrew S. Mackie, MD,[y] Samuel Menahem, MD, DMedHSc,[z] Maryanne Caruana, MD, PhD,[aa] Gruschen Veldtman, MD,[ab] Alexandra Soufi, MD,[ac] Susan M. Fernandes, LPD, PA-C,[ad] Kamila White, PhD,[ae] Edward Callus, PhD,[af,ag] Shelby Kutty, MD, PhD,[ah,ai] Fouke Ombelet, MSc,[a] Silke Apers, PhD,[a] and Adrienne H. Kovacs, PhD;[aj,ak] on behalf of the APPROACH-IS Consortium and the International Society for Adult Congenital Heart Disease (ISACHD)

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

See editorial by Greenway, pages 186–187 of this issue.

Received for publication February 13, 2020. Accepted March 29, 2020.

Corresponding author: Dr Philip Moons, KU Leuven Department of Public Health and Primary Care, Kapucijnenvoer 35, Box 7001, B-3000 Leuven, Belgium. Tel.: +32 16 373315.

E-mail: philip.moons@kuleuven.be

See page 222 for disclosure information.

https://doi.org/10.1016/j.cjca.2020.03.044

ABSTRACT

Background: We compared physical functioning, mental health, and quality of life (QoL) of patients with different subtypes of congenital heart disease (CHD) in a large international sample and investigated the role of functional class in explaining the variance in outcomes across heart defects.

Methods: In the cross-sectional **A**ssessment of **P**atterns of **P**atient-**R**eported **O**utcome in **A**dults with **C**ongenital **H**eart Disease-**I**nternational **S**tudy (APPROACH-IS), we enrolled 4028 adult patients with CHD from 15 countries. Diagnostic groups with at least 50 patients were included in these analyses, yielding a sample of 3538 patients (median age: 32 years; 52% women). Physical functioning, mental health, and QoL were measured with the SF-12 health status survey, Hospital Anxiety and Depression Scale (HADS), linear analog scale (LAS) and Satisfaction with Life Scale, respectively. Functional class was assessed using the patient-reported New York Heart Association (NYHA) class. Multivariable general linear mixed models were applied to assess the relationship between the type of CHD and patient-reported outcomes, adjusted for patient characteristics, and with country as random effect.

Results: Patients with coarctation of the aorta and those with isolated aortic valve disease reported the best physical functioning, mental health, and QoL. Patients with cyanotic heart disease or Eisenmenger syndrome had worst outcomes. The differences were statistically significant, above and beyond other patient characteristics. However, the explained variances were small (0.6% to 4.1%) and decreased further when functional status was added to the models (0.4% to 0.9%).

Conclusions: Some types of CHD predict worse patient-reported outcomes. However, it appears that it is the functional status associated with the heart defect rather than the heart defect itself that shapes the outcomes.

RÉSUMÉ

Introduction : Nous avons comparé le fonctionnement physique, la santé mentale et la qualité de vie (QV) des patients atteints de différents sous-types de cardiopathies congénitales (CC) d'un vaste échantillon international et examiné le rôle de la classe fonctionnelle pour expliquer la variance des résultats lors d'anomalies cardiaques.

Méthodes : Dans l'étude transversale internationale APPROACH-IS (pour **A**ssessment of **P**atterns of **P**atient-**R**eported **O**utcome in **A**dults with **C**ongenital **H**eart Disease-**I**nternational **S**tudy), nous avons inscrit 4 028 patients adultes atteints de CC de 15 pays. Nous avons inclus dans ces analyses les groupes de diagnostic d'au moins 50 patients qui formaient un échantillon de 3 538 patients (âge médian : 32 ans; 52 % de femmes). Le fonctionnement physique, la santé mentale et la QV ont fait respectivement l'objet de mesures au moyen de l'enquête sur l'état de santé SF-12, de l'échelle de dépression et d'anxiété en milieu hospitalier (HADS, de l'anglais Hospital Anxiety and Depression Scale), de l'échelle analogue linéaire (EAL) et de l'échelle de satisfaction de vie. Nous avons évalué la classe fonctionnelle à l'aide de la classe de la New York Heart Association (NYHA) que rapportaient les patients. Nous avons appliqué les modèles linéaires généralisés à plusieurs variables pour évaluer la relation entre le type de CC et les résultats rapportés par les patients, ajustés selon les caractéristiques des patients et le pays comme variable aléatoire.

Résultats : Les patients qui avaient une coarctation de l'aorte et ceux qui avaient une maladie valvulaire aortique isolée ont rapporté un fonctionnement physique, une santé mentale et une QV meilleurs. Les patients atteints d'une cardiopathie cyanotique ou du syndrome d'Eisenmenger avaient de plus mauvais résultats. Les différences étaient importantes sur le plan statistique, bien au-delà d'autres caractéristiques des patients. Toutefois, les variances expliquées étaient petites (de 0,6 % à 4,1 %) et diminuaient davantage lorsque l'état fonctionnel était ajouté aux modèles (de 0,4 % à 0,9 %).

Conclusions : Certains types de CC permettent de prédire de plus mauvais résultats rapportés par les patients. Toutefois, il semble que ce soit l'état fonctionnel associé à l'anomalie cardiaque plutôt que l'anomalie cardiaque elle-même qui façonne les résultats.

Over the past 4 decades, research on quality of life (QoL) in persons with congenital heart disease (CHD) has grown exponentially.[1] The mounting interest in QoL among affected patients coincided with increasing longevity.[2] Indeed, after the dramatic improvements in patient survival in the second half of the 20th century, clinicians and researchers were intrigued by the question of what the lives of patients with CHD looked like and whether the heart defect itself had a direct impact on QoL.[1]

Together with increased interest in QoL, there has been rising awareness of the importance of patient-reported health status.[3] It has been argued that patients' perspectives should be routinely incorporated within health metrics.[3] Perceived health, from both physical and mental perspectives, ought to be evaluated to obtain a comprehensive view of patient status. Further, in different cardiac populations, patient-reported outcomes are found to be independent predictors of mortality.[3]

There are previous studies that have indicated that a higher complexity of CHD is associated with poorer physical functioning and QoL.[4,5] However, within complexity categories, there may be large variation in outcomes according to the type of CHD. For instance, in 1 study, adults with transposition of the great arteries (TGAs) had an average SF-36 physical functioning of 93 on a scale from 0 (worst) to 100 (best),[6] whereas in another study, patients with single-ventricle physiology had much lower average physical functioning scores of 81.6.[7] This is meaningful because both of these subtypes are categorized as complex heart defects.[8] Conversely, there are examples in which similar patient-reported outcomes have been observed among patients with defects of great vs moderate complexity. To illustrate, cohorts of patients who have undergone atrial switch operations for TGA (categorized as a defect of great complexity) and patients with repaired tetralogy of Fallot (a defect of moderate complexity) both reported average scores on a QoL linear analog scale of 80 on a scale from 0 (worst QoL) to 100 (best QoL).[9,10] These apparent inconsistencies warrant direct comparison of the physical functioning and QoL of patients with specific heart defects. Such studies, however, have been scarce, primarily because large sample sizes are needed to have sufficient patients for each diagnostic group.

The aims of the current study, therefore, were to compare the physical functioning, mental health, and QoL in patients

with different heart defects, drawn from a large international sample, and to investigate to what extent the outcome variance is predicted by patients' functional class rather than the heart defect itself.

Methods

Study population and procedure

From 2013 to 2015, we conducted the **A**ssessment of **P**atterns of **P**atient-**R**eported **O**utcomes in **A**dults with **C**ongenital **H**eart Disease-**I**nternational **S**tudy (APPROACH-IS). This was a cross-sectional study involving 15 countries from 5 continents: Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Sweden, Switzerland, Taiwan, The Netherlands, and the United States [11] Patients we eligible for study inclusion if they met the following criteria: (1) diagnosis of CHD; (2) aged $\geq$18 years; (3) diagnosis established before adolescence; (4) continued follow-up at a CHD centre or included in a national/regional registry; and (5) physical, cognitive, and language capabilities required to complete self-report questionnaires. Patients with previous heart transplantation or primary pulmonary hypertension were excluded.[11] Patients who met inclusion criteria were contacted by mail or were approached during outpatient visits. Overall, 4028 adults with CHD were enrolled in APPROACH-IS.[12] For the current study, only diagnostic groups having at least 50 patients were included in the analyses, yielding a sample of 3538 patients (88% of the total recruited sample).

The study was conducted in keeping with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Hospitals Leuven/KU Leuven Belgium (coordinating centre) and by the local institutional review boards of the participating centres (when required). All participants provided written informed consent. Detailed information on the rationale, design, and methods of APPROACH-IS can be found in a dedicated methods paper.[11]

Measures

Patient characteristics included demographic data, such as sex, age, marital status, educational level, employment status, and patient-reported New York Heart Association (NYHA) functional class, which were collected using a self-report questionnaire. Specific diagnoses, as well as the complexity of the patients' heart defects (simple, moderate, or great complexity), were extracted from the medical records.

Self-reported physical functioning was measured using the Physical Component Summary (PCS) of the 12-item Short Form Health Survey (SF-12).[13] The score ranges from 0 to 100, with higher scores representing better physical functioning. Mental health was assessed using the Mental Component Summary (MCS) of the SF-12 [13] which also ranges from 0 to 100, and the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS), which range from 0 to 21.[14] Whereas higher SF-12 scores represent better physical and mental health status, higher scores on the HADS anxiety and depression subscales reflect greater symptoms. QoL was evaluated using a Linear Analog Scale (LAS)[15] and the Satisfaction With Life Scale.[16] The LAS ranges from 0 (worst imaginable QoL) to 100 (best imaginable QoL) and the Satisfaction With Life Scale ranges from 5 (extremely dissatisfied) to 35 (extremely satisfied). Supplemental Table S1 provides an expanded definition of the variables measured as well as the interpretation of scores for the individual questionnaires.

Statistical analyses

Continuous data are presented as means and standard deviations if normally distributed and as medians and interquartile ranges if not normally distributed. Categorical variables are represented by percentages. Multivariable general linear mixed models (GLMMs) were applied to assess the relationship between the type of CHD and physical functioning, mental health, and QoL adjusted for patient characteristics (age, sex, educational status, employment status, and marital status) and with country as a random effect. These patient characteristics have previously been related to patient-reported outcomes.[17] The heart defect with the highest score on the respective outcomes was used as reference group. A (pseudo) R^2 statistic was derived from the model χ^2.[18] This is an approximate estimate for the percentage of explained variance. When reported for the effect of the type of heart defect, these approximations are analogous to the semipartial R^2.

Data were visualized using ridgeline plots, expressing the density of the distribution of scores for the different heart defects (see Supplemental Box S1 for more details). To investigate the clinical difference between the respective heart defects and the reference group (= highest score), we calculated the standardized effect size (Cohen's *d*) for each type of defect and reported it in terms of absolute standardized effect size. The following cutoff values were used: 0.2 to 0.5, indicative of a small effect; 0.5 to 0.8, a moderate effect; and >0.8, a large effect.[19]

The proportion of missing values in the outcomes was small (5% to 8%). Therefore, multiple imputation was not used to address missing values, as this would unnecessarily complicate data analysis, and only patients for whom full data were available for all variables of interest were included in the GLMM. Data analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY). Ridgeline plots were made using Rstudio, version 1.1.463. A *P* level <0.05 was used as the cutoff for statistical significance, and statistical tests were 2-sided.

Results

Sample characteristics

The current sample was composed of 3538 patients with a median age of 32 years, and 52% were women. The majority of patients had high school degrees, worked part or full time, and were married or living with partners. With regard to medical characteristics, 49% had CHD of moderate complexity, and 55% reported that they were in NYHA functional class I (ie, asymptomatic). Demographic and medical characteristics of the sample are described in Supplemental Table S2 and were consistent with those of the larger sample included in APPROACH-IS.[12] The distribution

of the NYHA functional class in the different subtypes of CHD is described in Supplemental Table S3.

Physical functioning

Patients with coarctation of the aorta received the highest mean score on the physical component summary (83.6 ± 17.2), whereas patients with cyanotic heart disease or Eisenmenger syndrome had the lowest mean score (53.5 ± 21.8). The ridgeline plot shown in Figure 1 visually demonstrates that scores of patients with cyanotic heart disease/Eisenmenger syndrome were lower than those of other types of heart defects. When adjusted for patient characteristics, general linear mixed models showed that physical functioning was significantly lower in 12 heart defects compared with coarctation of the aorta (Fig. 1). The type of heart defect explained 3.9% of the variance of the physical component summary. When NYHA functional class was added to the model, the semipartial R^2 for the type of heart defect dropped to 0.8%, whereas the semipartial R^2 for NYHA was 36.5%.

As demonstrated in the bar chart in Figure 1, scores of patients with cyanotic heart disease/Eisenmenger syndrome differed with a large standardized effect size from the reference group: namely, patients with coarctation of the aorta. For patients with congenitally corrected TGA, pulmonary atresia, Fontan circulation, and Ebstein anomaly, a moderate difference was found with the reference group. A small difference was observed for several other diagnoses, as shown in Figure 1.

Mental health

In patients with coarctation of the aorta, the highest mean score on the mental component summary (76.3 ± 16.7) and the lowest mean score for depression (2.5 ± 2.7) were observed (Fig. 2). Patients with isolated aortic valve disease had the lowest level of anxiety (4.7 ± 3.8). People with cyanotic heart disease/Eisenmenger syndrome consistently had the worst scores on mental health (61.2 ± 20.2), depression symptoms (7.5 ± 4.6), and anxiety symptoms (5.2 ± 4.1). For the mental component summary, patients with TGA, Fontan circulation, cyanotic heart disease/Eisenmenger syndrome, or repaired ductus arteriosus/atrial and ventricular septal defects (ASD/VSD) had significantly lower scores compared with the reference group, adjusted for patient characteristics. Patients with TGA, Fontan circulation, or cyanotic heart disease/Eisenmenger syndrome scored significantly lower than the reference group for anxiety symptoms. Patients with TGA, pulmonary atresia, Fontan circulation, cyanotic heart disease/Eisenmenger syndrome, or atrioventricular septal defect/ostium primum ASD scored significantly lower than the reference group in depression symptoms (Fig. 2). The explained variance for the mental component summary, anxiety and depression was 1%, 1%, and 0.7%, respectively. When adjusted for NYHA class, the semipartial R^2 for the type of heart defect declined to 0.7%, 0.4%, and 0.5%, respectively. The semipartial R^2 for NYHA was 14.4% for the mental component summary, 7.2% for anxiety, and 9.9% for depression.

Effect sizes (Fig. 2) showed that the difference between the mental component summary of patients with cyanotic heart disease/Eisenmenger syndrome and the reference group was large. The difference was moderate for anxiety in patients with Fontan circulation and cyanotic heart disease/Eisenmenger syndrome. A large difference was also found for depression in patients with cyanotic heart disease/Eisenmenger syndrome. For the other differences, the effects were small or negligible (Fig. 2).

Quality of life

Patients with isolated aortic valve disease had the highest QoL score, both on the LAS (82.0 ± 13.8) and the Satisfaction with Life Scale (27.1 ± 6.0). Patients with cyanotic heart disease/Eisenmenger syndrome reported the lowest scores on QoL (67.1 ± 21.8; 22.4 ± 7.1) (Fig. 3). Compared with the reference group, a significantly lower score on the LAS was observed in patients with congenitally corrected TGA, Fontan circulation, cyanotic heart disease/Eisenmenger syndrome, and conduits. On the Satisfaction with Life Scale, patients with complete TGA, Fontan circulation, and cyanotic heart disease/Eisenmenger syndrome scored significantly lower when adjusted for patient characteristics. The semipartial R^2 for the type of heart defect on the LAS was 1.1% and on the Satisfaction with Life Scale 1.4%. These explained variances dropped to 0.4% and 0.6%, respectively, when NYHA class was added to the generalized linear mixed model. On the other hand, semipartial R^2 for NYHA was 10.7% for the LAS and 7.1% for the Satisfaction with Life Scale.

The effect size for the score on the LAS in patients with cyanotic heart disease/Eisenmenger syndrome was large and moderate for people with congenitally corrected TGA. On the Satisfaction with Life Scale, a moderate effect was found in patients with Fontan circulation and cyanotic heart disease/Eisenmenger syndrome. The other effects were small or negligible (Fig. 3).

Discussion

This was the first study in which the wide spectrum of CHD subtypes was compared using a comprehensive set of patient-reported outcomes. Most previous studies investigating patient-reported outcomes collapsed across a heterogeneous group of heart defects or focused on 1 particular heart lesion.[1] Few studies compared outcomes between 2 subtypes of heart defects. In these studies, heart defects of different complexity levels were compared,[20-22] or different interventions for the same condition were compared.[23] The current study demonstrated that patients with isolated aortic valve disease or coarctation of the aorta had the best scores on patient-reported outcomes, whereas patients with cyanotic heart disease/Eisenmenger syndrome consistently scored lowest.

It may be surprising that people with coarctation of the aorta report such positive patient-reported outcomes, as it is a categorized as a heart defect of moderate complexity. However, it has been shown that exercise capacity long term after treatment for coarctation of the aorta is preserved and comparable with healthy controls.[24] Within the adult population of CHD, patients with coarctation of the aorta seem to have the best capacity for exercise,[25] which is likely to reflect good physical functioning. Further, mental health among patients within this CHD subgroup has been found to be comparable with the scores of a healthy population,[26] and the proportion of patients with coarctation of the aorta who developed

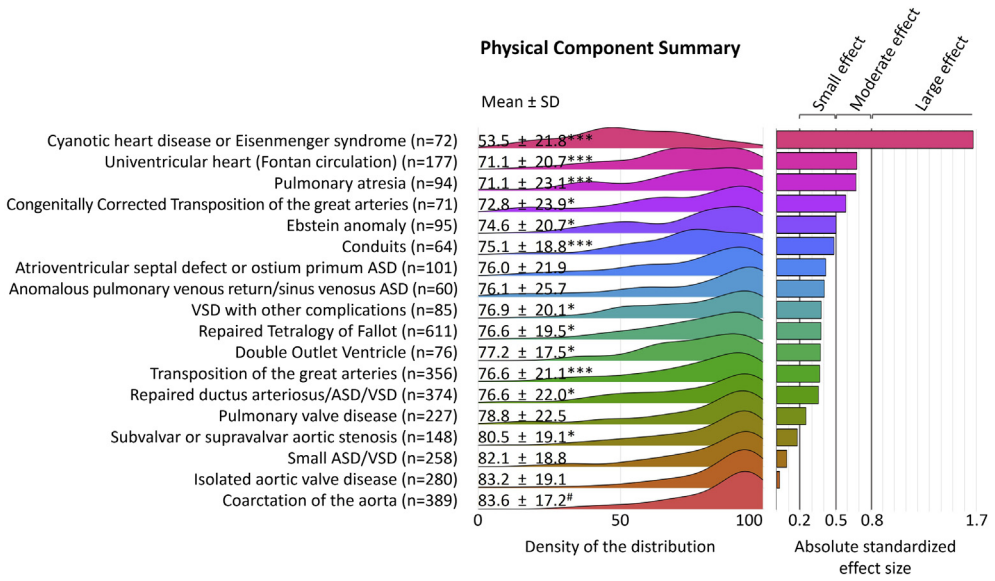


Figure 1. Physical functioning in patients with different heart defects and comparison with the heart defect with the highest score. ASD, atrial septal defect; VSD, ventricular septal defect.

depression (1.5%) was the lowest when compared with other heart defects.[27] A potential explanation for this finding is that coarctation of the aorta is usually treated without cardiopulmonary bypass, and therefore the risk for neurologic and cognitive side effects is lower. Overall, these findings suggest that patients with coarctation of the aorta and isolated aortic valve disease could be equally considered as reference groups as those with ASD or VSD, which have sometimes been used as a "healthy" comparison group.

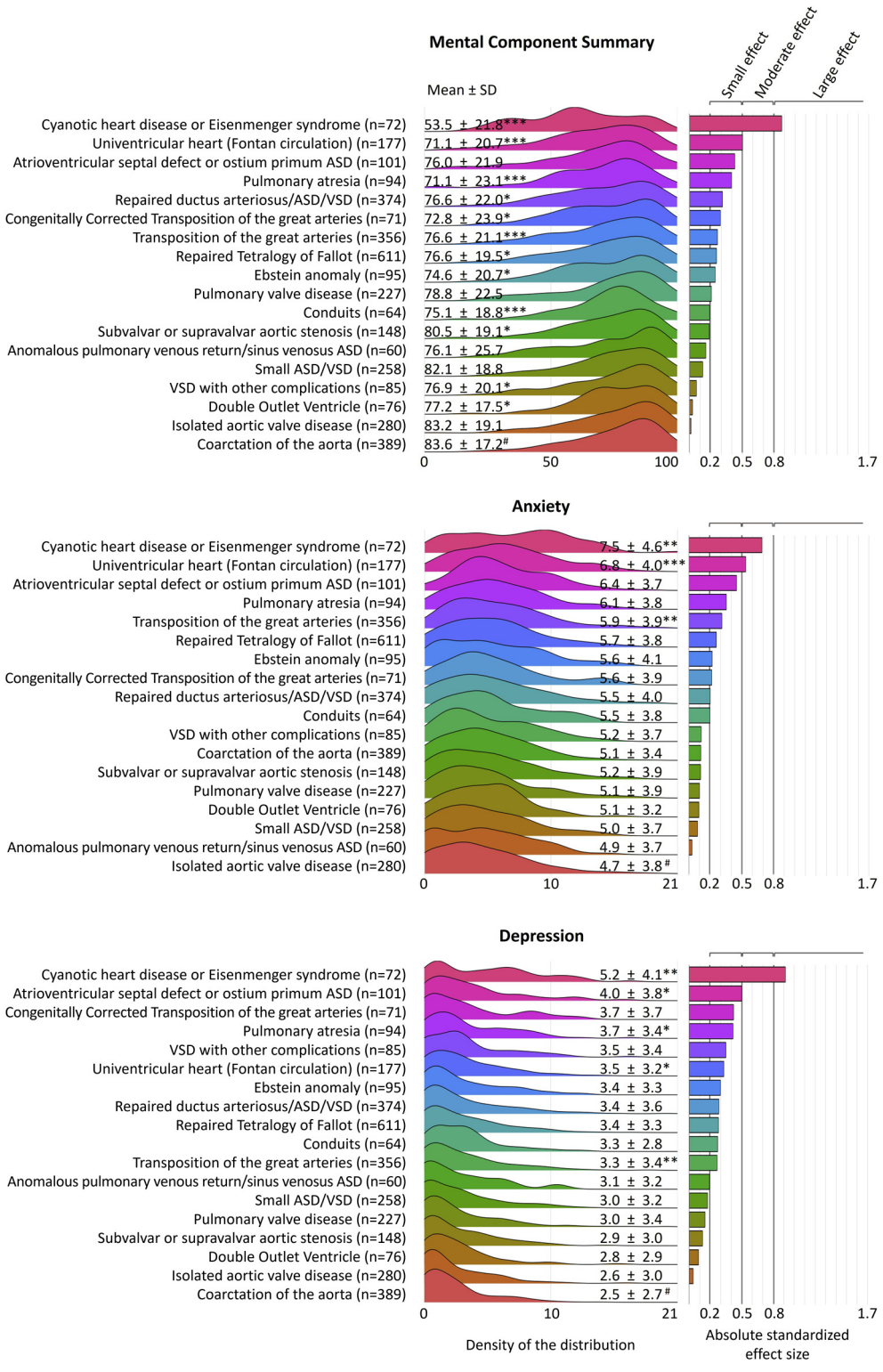
The fact that people with cyanotic heart defects and Eisenmenger syndrome received lowest scores on all patient-reported outcomes was anticipated. Research and clinical experiences indicate that these patients have significantly impaired exercise capacity.[25,28] The level of anxiety in these patients was high and was in keeping with the findings of a large-scale study in patients with Eisenmenger in France.[29] The level of depression in cyanotic heart disease/Eisenmenger syndrome in APPROACH-IS was actually even higher than that in the French cohort.[29]

Despite reaching statistical significance, the explained variance of the type of heart defect on the respective outcomes was small (0.7% to 3.9%). When adjusted for NYHA functional class, the explained variance was even smaller (0.4% to 0.8%), whereas the explained variance of the NYHA ranged from 7.1% to 36.5%. This shows that the functional impact of the heart defect, rather than the heart defect itself, affects patient-reported outcomes. This was most pronounced for physical health status. In line with these findings, it is understandable that the 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of adults with CHD proposed a new classification scheme, in which both anatomic complexity and current physiological stage of the patient are included: the so-called ACHD-AP score.[8] The first validity evaluation showed that adding the physiological component to anatomic complexity is better able to predict 15-year mortality.[30] Other functional indices, such as the Congenital Heart Disease Functional Index, also seem more predictive than anatomic classifications.[31] The relationship between functional indices and QoL was found to be larger compared with anatomic complexity and QoL.[32]

Findings of this study can inform clinicians about patient-reported outcomes as perceived by patients with different subtypes of CHD. Subgroups of patients with specific defects who may be prone to developing worse outcomes have been identified. The current study also carries implications for research. Results from this large international sample may serve as a benchmark for previous and future studies on patient-reported outcomes. For instance, this study demonstrates that the composition of the sample may have impact on the outcomes of the study. Indeed, an over-representation of patients with coarctation of the aorta or isolated aortic valve disease would now be expected to inflate scores and may lead to an overestimation of the status of patients with CHD. Further, investigators should not assume that patient-reported outcomes vary by defect complexity in a linear fashion, as, in this study, a moderately complex defect—namely, coarctation of the aorta—was associated with better outcomes than various mild heart lesions.

Methodological considerations

The current study has several strengths. We included more than 3500 patients from 15 countries; we had a high degree of complete data; and we used valid and reliable instruments to assess the self-reported outcomes comprehensively in this international sample. For the current study, we conducted multilevel analysis and adjusted for patient characteristics that



 # CHD with highest score as reference
** Statistically significant difference with reference in general linear mixed models adjusted for patient characteristics: *p<0.05; **p<0.01; ***p<0.001*

Figure 2. Mental health in patients with different heart defects and comparison with the heart defect with the highest score. ASD, atrial septal defect; VSD, ventricular septal defect.

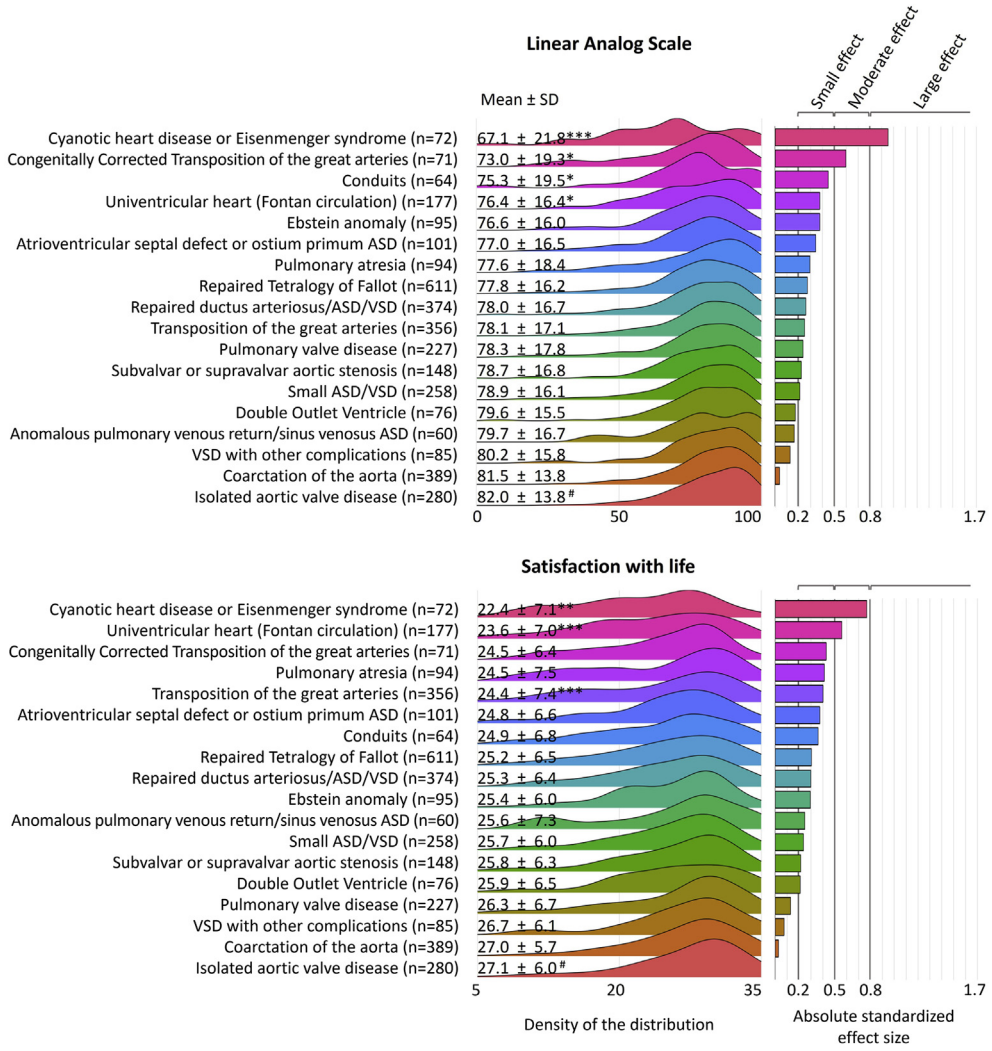


Figure 3. Quality of life in patients with different heart defects and its comparison with the heart defect with the highest score. ASD, atrial septal defect; VSD, ventricular septal defect.

have been shown to predict patient-reported outcomes.[17] In addition to statistical significance, we also reported effect sizes, which allowed us to appraise the magnitude of the differences in a standardized way. The visualization technique of the ridgeline plots provides insights into the density of distribution of scores, which extends the typical reporting of central tendency and dispersion measures.

However, we have to bear in mind some limitations inherent to APPROACH-IS that may hamper generalizability. It was a cross-sectional study (not allowing conclusions in terms of causality); for most participating countries, data from only 1 centre were available; patients who were physically or mentally incapable of completing the questionnaires were not represented; and there was no healthy control group.[17] A control group could have allowed us to put our findings more into perspective. However, a meta-analysis comprising 234 studies indicated that patients with moderate or complex CHD generally have worse physical functioning yet equal mental health, compared with healthy persons.[4] Patients with mild heart defects did not differ from healthy persons.[4]

For the current study, defects with very low prevalence—such as truncus arteriosus, tricuspid atresia or pulmonary atresia that were not treated with a Fontan operation, and infundibular right ventricular outflow obstruction—were not included in the analyses. These less prevalent heart defects accounted for 12% of the APPROACH-IS sample. Future studies in adults with CHD will also include patients with heart defects that were lethal in infancy until 2 decades ago, such as hypoplastic left heart syndrome, because more of these patients are now reaching adulthood. The categorization of CHD used in this study was mutually exclusive. The most severe defect was reported, not including combinations with other heart lesions (eg, TGA with VSD). Further, the current study did not allow an investigation of the impact of different treatment strategies. For instance, it could be interesting to compare the outcomes of patients with different surgical

approaches for the same lesion (eg, ventriculotomy vs transatrial/transpulmonary approach in tetralogy of Fallot). The type of operation, or the specifics on the material used, was not available in APPROACH-IS. Finally, we did not measure extracardiac drivers for outcomes. Some syndromes may have systemic and neurocognitive consequences having impact on physical functioning, mental health, and QoL.[33] Health behaviours, such as smoking, drug use, and consumption of alcohol, also may have a differential impact on outcomes in different heart defects.[34,35] These are avenues for future research.

Conclusions

This large-scale international study showed that some types of CHD predict worse patient-reported outcomes. However, the outcomes were shaped by the functional status associated with the heart defect rather than the heart defect itself. Indeed, the explained variances of the subtype of heart defect were small and decreased further when the functional status was added to the models. Hence, it is important that patients are not only classified based on their anatomic complexity but also on their current physiological and functional status.

Acknowledgements

The authors wish to thank the APPROACH-IS participants who made this study possible. In addition, they would like to thank everyone at the participating centres who made substantial contributions to APPROACH-IS. The full list of collaborators in the APPROACH-IS consortium is provided in Supplementary Box S2.

Funding Sources

This work was supported 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 CCF201302 (to H.L.Y.). This work was endorsed by, and conducted in collaboration with, the International Society for Adult Congenital Heart Disease. **Registration**: ClinicalTrials.gov: NCT02150603.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Bratt EL, Moons P. Forty years of quality-of-life research in congenital heart disease: Temporal trends in conceptual and methodological rigor. Int J Cardiol 2015;195:1-6.
2. Moons P, Luyckx K. Quality-of-life research in adult patients with congenital heart disease: current status and the way forward. Acta Paediatr 2019;108:1765-72.
3. Rumsfeld JS, Alexander KP, Goff DC Jr, et al. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. Circulation 2013;127:2233-49.
4. Kahr PC, Radke RM, Orwat S, Baumgartner H, Diller GP. Analysis of associations between congenital heart defect complexity and health-related quality of life using a meta-analytic strategy. Int J Cardiol 2015;199:197-203.
5. Ladak LA, Hasan BS, Gullick J, Gallagher R. Health-related quality of life in congenital heart disease surgery in children and young adults: a systematic review and meta-analysis. Arch Dis Child 2019;104:340-7.
6. Opic P, Utens EM, Ruys TP, et al. Long-term psychosocial outcome of adults with tetralogy of Fallot and transposition of the great arteries: a historical comparison. Cardiol Young 2014;24:593-604.
7. Overgaard D, Schrader AM, Lisby KH, et al. Patient-reported outcomes in adult survivors with single-ventricle physiology. Cardiology 2011;120:36-42.
8. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e81-192.
9. Moons P, De Bleser L, Budts W, et al. Health status, functional abilities, and quality of life after the Mustard or Senning operation. Ann Thorac Surg 2004;77:1359-65. discussion 1365.
10. Dulfer K, Duppen N, Kuipers IM, et al. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial. J Adolesc Health 2014;55:65-72.
11. Apers S, Kovacs AH, Luyckx K, et al. 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.
12. Apers S, Kovacs AH, Luyckx K, et al. Quality of life of adults with congenital heart disease in 15 countries: evaluating country-specific characteristics. J Am Coll Cardiol 2016;67:2237-45.
13. Ware JE, Kosinski M, Turner-Bowker DM, Sundaram M, Gandek B, Maruish ME. User's Manual for the SF-12v2 Health Survey, Second Edition. Lincoln, RI: QualityMetric, Incorporated, 2009.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
15. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil 2006;13:407-13.
16. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction with Life Scale. J Pers Assess 1985;49:71-5.
17. Moons P, Kovacs AH, Luyckx K, et al. Patient-reported outcomes in adults with congenital heart disease: inter-country variation, standard of living and healthcare system factors. Int J Cardiol 2018;251:34-41.
18. Shtatland E, Moore S, Barton M. Why we need an R2 measure of fit (and not only one) in proc logistic and proc genmod. SUGI 2000 Proceedings. 2000; paper 256-226.
19. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum, 1988.
20. Ternestedt BM, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect. Pediatr Cardiol 2001;22:128-32.

21. Fogleman ND, Apers S, Moons P, et al. Regional variation in quality of life in patients with a Fontan circulation: a multinational perspective. Am Heart J 2017;193:55-62.

22. Holbein CE, Fogleman ND, Hommel K, et al. A multinational observational investigation of illness perceptions and quality of life among patients with a Fontan circulation. Congenit Heart Dis 2018;13:392-400.

23. Muller J, Hess J, Horer J, Hager A. Persistent superior exercise performance and quality of life long-term after arterial switch operation compared to that after atrial redirection. Int J Cardiol 2013;166:381-4.

24. Dijkema EJ, Sieswerda GT, Breur J, Haas F, Slieker MG, Takken T. Exercise capacity in asymptomatic adult patients treated for coarctation of the aorta. Pediatr Cardiol 2019;40:1488-93.

25. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease: relation to activities of daily life—single centre experience and review of published data. Eur Heart J 2012;33:1386-96.

26. Bambul Heck P, Pabst von Ohain J, Kaemmerer H, Ewert P, Hager A. Quality of life after surgical treatment of coarctation in long-term follow-up (CoAFU): predictive value of clinical variables. Int J Cardiol 2018;250:116-9.

27. Muller J, Hess J, Hager A. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity. Int J Cardiol 2012;154:265-9.

28. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828-35.

29. Amedro P, Basquin A, Gressin V, et al. Health-related quality of life of patients with pulmonary arterial hypertension associated with CHD: the multicentre cross-sectional ACHILLE study. Cardiol Young 2016;26:1250-9.

30. Ombelet F, Goossens E, Van De Bruaene A, Budts W, Moons P. Newly developed adult congenital heart disease anatomic and physiological classification: first predictive validity evaluation. J Am Heart Assoc 2020;9:e014988.

31. Ombelet F, Goossens E, Apers S, Budts W, Gewillig M, Moons P. Predicting 15-year mortality in adults with congenital heart disease using disease severity and functional indices. Can J Cardiol 2019;35:907-13.

32. Moons P, Van Deyk K, De Geest S, Gewillig M, Budts W. Is the severity of congenital heart disease associated with the quality of life and perceived health of adult patients? Heart 2005;91:1193-8.

33. Keir M, Ebert P, Kovacs AH, et al. Neurocognition in adult congenital heart disease: how to monitor and prevent progressive decline. Can J Cardiol 2019;35:1675-85.

34. Holbein CE, Peugh J, Veldtman GR, et al. Health behaviours reported by adults with congenital heart disease across 15 countries. Eur J Prev Cardiol 2020:2047487319876231.

35. Moons P, Luyckx K, Kovacs AH, et al. Prevalence and effects of cigarette smoking, cannabis consumption, and co-use in adults from 15 countries with congenital heart disease. Can J Cardiol 2019;35:1842-50.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2020.03.044.