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Regional variation in quality of life in patients with a Fontan circulation - A multinational perspective

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1 Title Page

1.1 Title

Regional variation in quality of life in patients with a Fontan circulation - A multinational perspective

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2 Abstract and Keywords

2.1 Background: Impaired quality of life (QOL) is associated with congenital heart disease (CHD) and country of residence; however, few studies have compared QOL in patients with differing complexities of CHD across regional populations. The current study examined regional variation in QOL outcomes in a large multinational sample of patients with a Fontan relative to patients with atrial septal defects (ASD) and ventricular septal defects (VSD).

2.2 Methods: From the Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study (APPROACH-IS) study, 405 patients (163 Fontan and 242 ASD/VSD) across Asia, Europe and North America provided consent for access to their medical records and completed a survey evaluating QOL (0 to 100 Linear Analog Scale). Primary CHD diagnosis, disease complexity, surgical history, and documented history of mood and anxiety disorders were recorded. Differences in QOL, medical complications, and mood and anxiety disorders between Fontan and ASD/VSD patients, and across geographic regions, were examined using ANCOVA. Hierarchical regression analyses were conducted to identify variables associated with the QOL ratings.

2.3 Results: Patients with a Fontan reported significantly lower QOL, and greater medical complications and mood and anxiety disorders relative to patients with ASD/VSD. Inpatient cardiac admissions, mood disorders and anxiety disorders were associated with lower QOL among patients with a Fontan and mood disorders were associated with lower QOL among patients with ASD/VSD. Regional differences for QOL were not observed in patients with a Fontan; however, significant differences were identified in patients with ASD/VSD.

2.4 Conclusion: Regional variation of QOL is commonplace in adults with CHD; however, it appears affected by greater disease burden. Among patients with a Fontan, regional variation of

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QOL is lost. Specific attempts to screen for QOL and mood and anxiety disorders among CHD patients may improve the care of patients with the greatest disease burden.

2.5 Keywords: Fontan circulation, congenital heart defects, single ventricle physiology, atrial septal defects, ventricular septal defects, quality of life

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3 Translational Perspective

Fontan patients have among the highest degree of disease complexity in individuals affected with congenital heart disease. During late follow-up, they have some of the highest rates of cardiac and extra-cardiac medical complications necessitating inpatient admission. This high disease burden very significantly affects QOL. Although this is a cross-sectional study examining QOL in a large multinational cohort of adult with congenital heart disease, concerted efforts should be made to screen for QOL and mood and anxiety disorders in those with greatest disease burden and proactively addressed.

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4 Introduction

The Fontan circulation, first described by Fontan and Baudet in 1971 as a surgical palliation for tricuspid atresia (1), has provided lifesaving palliation for individuals born with single ventricle physiology. The circulation redirects caval venous return directly into the pulmonary circulation without an intervening pump, thereby securing abolition of cyanosis and single ventricular volume overload. Survival outcomes of the Fontan circulation in the modern era are excellent with greater than 90% survival at 20 years (2). Following a Fontan circulation however, patients are at greater risk for thromboembolic events (3), multi-organ dysfunction (4), postoperative arrhythmia (5), myocardial dysfunction (6), impaired cardiac autonomic nervous activity (7), and heart failure (8). These late adverse outcomes all frequently require inpatient assessment and management, and may negatively affect quality of life (QOL) outcomes.

Current literature suggests that QOL outcomes in individuals with congenital heart disease (CHD) are affected not only by the CHD itself (9,10) but also by country of residence, such that individuals in North America and Europe report higher QOL outcomes relative to individuals in Asia (11). Although individuals with CHD are at an increased risk for adverse medical complications (3-8) and mood and anxiety disorders (12), few studies have examined whether medical complications and mood and anxiety disorders are associated with QOL outcomes in CHD populations (12). Furthermore, there remains a paucity of literature examining whether greater disease burden in CHD populations affects regional QOL outcomes. As observed in previous literature (11), it may be the case that all CHD patients, regardless of CHD complexity, follow a similar QOL regional variation.

In the present study we examine regional variation on QOL outcomes in Fontan patients (complex CHD) and compare and contrast this to patients with simple congenital heart defects,

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consisting of atrial septal defects (ASD) and ventricular septal defects (VSD). We hypothesize the following: (i) Fontan patients will report significantly lower QOL relative to ASD/VSD patients, (ii) Fontan patients will have significantly more medical complications and mood and anxiety disorders relative to ASD/VSD patients, (iii) Medical complications and mood and anxiety disorders will be associated with QOL outcomes in Fontan patients and ASD/VSD patients, and (iv) Fontan patients and ASD/VSD patients will demonstrate regional differences in QOL outcomes.

5 Methods

5.1 Project design and data collection procedures

APPROACH-IS is a cross-sectional study conducted on a large international sample. In collaboration with the International Society for Adult Congenital Heart Disease (ISACHD), this work was supported by KU Leuven (Belgium), the Swedish Heart and Lung Foundation (Sweden), the Gothenburg Person-Centered Care center (Sweden) and the Cardiac Children's Foundation (Taiwan). APPROACH-IS was created to investigate patient-reported outcomes in adults with congenital heart disease (CHD) worldwide and to identify cultural and geographic differences. The study design and data collection procedures were previously reported (13).

5.2 Settings

Participating centers for this multi-country project were selected by the APPROACH-IS steering committee based on feasibility, willingness to participate and geographical distribution. The current study included participants with a Fontan and ASD/VSD from 22 treatment centers across 13 countries (Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Taiwan, the Netherlands, Sweden, Switzerland, and United States of America) in three geographic regions (Asia, Europe and North America).

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5.3 Sample

For inclusion, patients were required to meet the following criteria: (i) diagnosis of ASD/VSD or had received a Fontan, (ii) 18 years of age or older; (iii) diagnosis established before the age of 10, (iv) continued follow-up at a CHD center or included in a national/regional registry; and (v) physical, cognitive, and language capabilities required to complete patient reported QOL measure. Patients were excluded from study participation if they (i) underwent prior heart transplantation; (ii) had primary pulmonary hypertension; or (iii) had impaired cognitive abilities.

5.4 Patient-reported measures and patient information

Patients completed a background information questionnaire focused on socio-demographic variables and a QOL measure. In APPROACH-IS, QOL was defined as "the degree of overall life satisfaction that is positively or negatively influenced by individuals' perception of certain aspects of life important to them, including matters both related and unrelated to health" (14). Using this conceptualization, QOL refers to a global perspective and is not limited to health-related factors. In line with this definition, the Linear Analog Scale (LAS) is extensively used as the method to rate overall QOL in CHD (15). The LAS is vertically oriented, 10-centimeter line graded with indicators from 0 (worst imaginable QOL) to 100 (best imaginable QOL; (15). The LAS existed in numerous languages, but additional translations were undertaken for APPROACH-IS. Some APPROACH-IS centers conducted cognitive interviews to confirm intelligibility of LAS; in these cases, the LAS translation was confirmed to be correct and intelligible. The LAS has demonstrated validity and reliability in adults with CHD (15).

To determine patient information such as demographic variables, medical complications (i.e., cardiac surgery, interventional cardiac catheterization, congestive heart failure, arrhythmia,

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other medical condition (i.e. concurrent medical condition), cardiac device (i.e. pacemaker and implantable cardioverter defibrillator), and inpatient cardiac admission), and mood and anxiety disorders, each patient provided consent for access to their medical records. One member, or a team of study nurses and/or research associates from each of the participating research centers reviewed patient medical records to determine (i) medical background of study participants and (ii) to investigate whether patient-reported outcomes vary as a function of medical complications or mood and anxiety disorders. Data abstraction included primary CHD diagnosis, disease complexity, and surgical history. Additionally, documented lifetime history of a mood disorder and an anxiety disorder was recorded. Specific mood and anxiety disorders were not recorded in the current study.

5.5 Ethical Issues

APPROACH-IS was approved by the Institutional Review Board (IRB) of the University Hospitals Leuven/KU Leuven, and also by the IRB of each participating center. The study protocol was recorded at ClinicalTrials.gov: NCT02150603.

5.6 Statistical Analyses

For hypothesis 1, given previous research suggesting that QOL ratings are associated with age, employment status and marital status (11), Analyses of Covariance (ANCOVAs) were employed to examine differences in QOL between Fontan patients and ASD/VSD patients while controlling for age, sex, employment status (i.e., full-time paid work or part-time paid work), and marital status (i.e., married or remarried). For hypothesis 2, ANCOVAs were employed to examine differences in medical complications and mood and anxiety disorders between Fontan patients and ASD/VSD patients while controlling for age and sex. For hypothesis 3, hierarchical linear regressions were conducted to identify variables (i.e., medical complications and/or mood

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and anxiety disorders) associated with QOL ratings in Fontan patients and ASD/VSD patients after controlling for age, sex, marital status and employment status. For hypothesis 4, ANCOVAs were employed to investigate differences in QOL between geographic region (i.e., Asia, Europe and North America) while controlling for age, sex, employment status, and marital status. All data was analyzed using SPSS® 22 software (Armonk, NY).

6 Results

6.1 Demographic and geographic regional distribution in Fontan patients and ASD/VSD patients

Four hundred and five patients were included in the current study, consisting of 163 Fontan patients (85 males, 78 females; *Mean* age=27.4±7.6 years) and 242 ASD or VSD patients (97 males; 145 females; *Mean* age=37.0±14.6 years; **Table 1**). Significant differences were observed for age, sex, and marital status, such that Fontan patients were significantly more likely to be younger (p<.001), male (p=.02), and not married (p=.001) relative to ASD/VSD patients **(see Table 1**).

Among patients in the current study, 69.1% described as White/Caucasian, 24.2% described as Asian, 1.5% described as Black/African-American, 1.5% described as Middle-Eastern/Arabic, 1.0% described as Hispanic/Latino, and 0.5% described as identifying with another ethnical background.

By continent, participants were enrolled from Asia, Europe, and North America. Significant differences were observed for geographic regional distribution (p<.001) between Fontan and ASD/VSD patients, such that a majority of participants were from Europe.

6.2 QOL ratings in Fontan patients and ASD/VSD patients

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On the LAS, Fontan patients (76.4±16.4) reported lower mean ratings relative to ASD/VSD patients (80.0±14.0). When adjusted for age, sex, employment status, and marital status, this difference was statistically significant (p=.03), confirming our hypothesis 1.

6.3 Medical complications and mood and anxiety disorders in Fontan patients and ASD/VSD patients

After controlling for age and sex, Fontan patients were significantly more likely to experience medical complications and mood and anxiety disorders relative to patients with ASD/VSD (**Table 2**). Overall, 28.2% of the Fontan patients had a documented mood or anxiety disorder or both. In ASD/VSD patients, this proportion was 7.0%. Hence, we could confirm our hypothesis 2.

6.4 Medical complications and mood and anxiety disorders associated with QOL ratings in Fontan patients and ASD/VSD patients.

Hierarchical linear regression analyses in Fontan patients demonstrated that greater inpatient cardiac admissions (p=.01), mood disorders (p=.02) and anxiety disorders (p=.02) were negatively associated with QOL (**Table 3**). In ASD/VSD patients, greater mood disorders (p=.03) were negatively associated with QOL. All other variables were not significantly associated with QOL in either cohort. Thus, we were partly able to confirm hypothesis 3, as some but not all, medical complications and mood and anxiety disorders were associated with QOL outcomes among Fontan and ASD/VSD patients.

6.5 Regional variation in QOL ratings in Fontan patients and ASD/VSD patients

Figure 1 illustrates the mean LAS scores for Fontan and ASD/VSD patients by region. When adjusted for age, sex, employment status, and marital status, in Fontan patients, there were no significant differences in LAS ratings across regions (p=.90). On the other hand, in ASD/VSD

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patients, LAS ratings were significantly affected by region (p=.01), such that patients with ASD/VSD in North America and Europe reported higher QOL ratings than patients in Asia (**See Fig. 1**). This finding suggests that the complexity of the condition could be a moderator for the relationship between region and QOL. This moderator effect was significant, such that regional variation was more strongly related to QOL among ASD/VSD patients rather than Fontan patients (p=.05). Hence, we partly rejected hypothesis 4, in which we expected regional variation, both in Fontan and in ASD/VSD patients.

7 Discussion

The current findings present an important step towards better delineation of QOL outcomes in an international sample of patients with single ventricle physiology palliated with a Fontan circulation. Confirming our hypothesis, Fontan patients reported lower QOL relative to ASD/VSD patients. This is consistent with previous research suggesting QOL ratings are impaired in Fontan patients (9, 10). Prior studies compared Fontan patients with healthy controls, whereas we compared them to ASD/VSD patients. Another difference is that the previous studies operationalized QOL in terms of physical and mental/psychosocial functioning (9, 10) whereas we defined and measured QOL as overall satisfaction with life. However, irrespective the different conceptual approaches (16), the findings are consistent. It is important to note that QOL differences between Fontan patients and ASD/VSD patients were statistically significant, but relatively small. Adults with CHD are generally satisfied with their lives (11), and complexity of the heart defect plays a marginal role (17). Factors that explain why patients with complex heart disease thrive in the face of adversity are critical to elucidate the good QOL in Fontan patients (18, 19). Indeed, Fontan patients may view themselves as both strong and healthy, with a special "commitment to life" (20).

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In the present study, we also demonstrated significantly more medical complications and mood and anxiety disorders in Fontan patients compared to ASD/VSD patients. The Fontan circulation is considered palliative procedure (21), and not surprisingly has a number of medical complications during late follow up. However, the four times higher proportion of mood and anxiety disorders documented in the medical records of Fontan patients compared to ASD/VSD patients was striking. This underscores the need for routine screening of mood and anxiety disorders, and integrating psychosocial monitoring and care in the standard follow-up of Fontan patients. Longitudinal assessments of depressive symptoms are advocated because persistence of depressive symptoms, which cannot be captured with cross-sectional evaluations, are found to have detrimental consequences (22).

The necessity for ad-hoc mental health screening services in addition to routine medical care is reinforced by the finding that Fontan patients' QOL is associated with prior mood and anxiety disorder. Also in ASD/VSD patients, the QOL is predicted by prior mood disorder. Previous research suggests that mood and anxiety disorders are associated with CHD (12) and lower QOL (22). More specifically, recent research by DeMaso and colleagues (23) suggests that regardless of genetic comorbidities, patients with a Fontan demonstrated higher rates of depressive and anxiety symptoms relative to healthy controls. Thus, mental health screening services may assist in identifying mood and anxiety disorders and may possibly improve QOL outcomes through treatment initiatives.

With regards to our hypothesis pertaining to the regional variation of QOL, our findings were mixed. The expected regional differences (11) were corroborated in ASD/VSD patients, but not in Fontan patients. Indeed, ASD/VSD patients in North America had higher QOL scores than patients living in Asia. The difference remained statistically significant after adjusting for

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potential confounders. In contrast however, Fontan patients reported similar QOL ratings across regions, suggesting that regional differences in QOL are lost in greater complexity CHD. Comparison of our findings with the literature is difficult, because there is a scarcity of studies examining QOL outcomes across regions of the world, and is in fact non-existent for Fontan patients to our knowledge. This was precisely the rationale for conducting APPROACH-IS. Speculatively and intuitively, it may be the case that in ASD/VSD patients living with a milder heart condition, QOL outcomes may be influenced by the day-to-day challenges that everyone experiences within the specific context of their regional locality. In contrast, when CHD severity is great, such as in Fontan patients, or in cases where specific medical complications and mood and anxiety disorders co-exist, regional variation is lost. Possible contributors to this phenomenon may be the higher occurrence of adverse events, and possible neuropsychiatric effects of compromised hemodynamics and/or mood states.

7.1 Limitations

Several limitations exist in this multinational study. Firstly, all data were obtained concurrently. We were therefore not able to determine if these differences exist over time preceding the study.

Secondly, as noted in Apers et al. (11), the current sample might be affected by selection bias, such that all patients in the study were recruited from participating centers. While previous studies have documented participants in APPROACH-IS and nonparticipants are relatively comparable groups (24), selection bias may not be completely excluded.

Thirdly, we did not investigate objective physical functioning nor did we investigate neuropsychiatric influences, associated defects or genetic syndromes on QOL or regional variation. Research suggests that the Fontan circulation is associated with reduced physical

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activity (25), below-average cognitive abilities (6) and genetic abnormalities (23). Further study is needed in these areas to determine the effects of physical functioning, neuropsychiatric performance and genetic comorbidities on QOL outcomes.

Fourthly, the current study relied on the use of LAS. Although it may be argued that the study may have benefitted from additional QOL measures, Apers and colleagues (11) demonstrated the LAS is consistent with other measurements of QOL and that the findings of inferential statistics would be largely the same when the Satisfaction with Life Scale would have been used. Furthermore, the LAS has demonstrated validity and reliability in adults with CHD (15).

Fifthly, while the current study suggests patients with a Fontan are more likely to have mood or anxiety disorders relative to patients with ASD/VSD, documentation of mood and anxiety disorders may be under reported relative to actual rates. Recent evidence suggests that 65% Fontan patients who were evaluated by a board-certified child psychiatrist following surgery had a lifetime psychiatric diagnosis, including 48% who have had a mood or anxiety disorder (23). While considerably higher than the rates in the current study, all data in this study were collected via medical chart review and it is possible psychiatric information did not make it into patient medical charts. Therefore, future studies may seek to replicate the methods proposed by DeMaso and colleagues (23). In case that systematic psychiatric evaluation is not feasible, longitudinal assessments of depressive symptoms are needed. Persistence of depressive symptoms, which cannot be captured with cross-sectional evaluations, are found to have detrimental consequences.

Sixthly, the current study did not include patient/family income as a covariate in our analyses as this information was not collected. Previous literature suggests family income may

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affect QOL among patients with a Fontan (26). However, in a global context, income as such is difficult to compare, and should be rather expressed in terms of purchasing power parity. Recent analyses of APPROACH-IS data at country level showed that the Gross Domestic Product based on purchasing power parity significantly predicted depressive symptoms and health risk behaviors (Moons et al, under review). The explained variance was however smaller than 1%.

Finally, APPROACH-IS was administered to participants located on five continents (i.e., Asia, Australia, Europe, North America and South America); however, the current study contains data from three continents only (i.e., Asia, Europe and North America) due to inadequate sample sizes from Australia (five patients with a Fontan circulation and four patients with ASD/VSD) and South America (eight patients with a Fontan circulation and five patients with ASD/VSD). As noted in Apers et al. (11), limited funding and logistics made it too difficult for African centers to participate. QOL analysis by specific countries in the sample were not possible due to inadequate sample sizes. Future studies should seek to expand the regional investigation of QOL outcomes in patients with CHD.

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8 Acknowledgements

8.1 Conflict of Interest

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors declare no conflicts of interest.

8.2 Declaration of Helsinki

The current study complies with the Declaration of Helsinki. APPROACH-IS was approved by the Institutional Review Board (IRB) of the University Hospitals Leuven/KU Leuven, and also by the IRB of each participating center. Obtained consent has been obtained from all participants.

8.3 Collaborators

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ACCEPTED MANUSCRIPT

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9 References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240-8.

2. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, Penny DJ, Brizard CP. The Fontan Procedure Contemporary Techniques Have Improved Long-Term Outcomes. Circulation 2007;116:I-157.

3. Rosenthal DN, Friedman AH, Kleinman CS, Kopf GS, Rosenfeld LE, Hellenbrand WE. Thromboembolic adverse outcomes after Fontan circulations. Circulation 1995;92:287-293.

4. Baek JS, Bae EJ, Ko JS, Kim GB, Kwon BS, Lee SY, Noh C, Park E, Lee W. Late hepatic adverse outcomes after Fontan circulation; non-invasive markers of hepatic fibrosis and risk factors. Heart 2010;96:1750-5.

5. Peters NS, Somerville J. Arrhythmias after the Fontan procedure. Br Heart J 1992;68:199-204.

6. Marino BS. Outcomes after the Fontan procedure. Curr Opin Pediatr 2002;14:620-6.

7. Ohuchi H, Hasegawa S, Yasuda K, Yamada O, Ono Y, Echigo S. Severely impaired cardiac autonomic nervous activity after the Fontan circulation. Circulation 2001;104:1513-8.

8. Piran S, Veldtman G, Siu S, Webb GD, Liu, PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation 2002;105:1189-1194.

9. van den Bosch AE, Roos-Hesselink JW, van Domburg R, Bogers AJ, Simoons ML, Meijboom FJ. (2004). Long-term outcome and quality of life in adult patients after the Fontan circulation. Am J Cardiol, 2004;93:1141-5.

10. Uzark K, Zak V, Shrader P, McCrindle, BW, Radojewski E, Varni, JW, Daniels K, Handisides J, Hill KD, Lambert LM, Margossian R, Pemberton VL, Lai WW, Atz AM. Assessment of Quality of Life in Young Patients with Single Ventricle after the Fontan Circulation. J Pediatr 2016;170:166-177.

11. Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, Sluman MA, Wang J, 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. (2016). Quality of life of adults with congenital heart disease in 15 countries: evaluating country-specific characteristics. J Am Coll Cardiol 2016;67:2237-45.

12. 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.

ACCEPTED MANUSCRIPT

13. 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 J, 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.

14. Moons P, Van Deyk K, Marquet K, Raes E, De Bleser L, Budts W, De Geest S. Individual quality of life in adults with congenital heart disease: a paradigm shift. Eur Heart J 2005;26:298-307.

15. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. 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. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. Int J Nurs Stud 2006;43:891-901.

17. 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.

18. Apers S, Rassart J, Luyckx K, Oris L, Goossens E, Budts W, Moons P, I-Detach Investigators. Bringing Antonovsky's salutogenic theory to life: A qualitative inquiry into the experiences of young people with congenital heart disease. Int J Qual Stud Health Well-being 2016;11:29346.

19. Apers S, Moons P, Goossens E, Luyckx K, Gewillig M, Bogaerts K, Budts W, i-DETACH investigators. Sense of coherence and perceived physical health explain the better quality of life in adolescents with congenital heart disease. Eur J Cardiovasc Nurs 2013;12:475-83.

20. Berghammer MC, Brink E, Rydberg AM, Dellborg M, Ekman I. Committed to Life: Adolescents' and Young Adults' Experiences of Living with Fontan Circulation. Congenit Heart Dis 2015;10:403-12.

21. Fontan F, Kirklin J W, Fernandez G, Costa F, Naftel DC, Tritto F, Blackstone EH. Outcome after a" perfect" Fontan circulation. Circulation 1990;81:1520-36.

22. Luyckx K, Rassart J, Goossens E, Apers S, Oris L, Moons P. Development and persistence of depressive symptoms in adolescents with CHD. Cardiol Young 2016;26:1115-22.

23. DeMaso, DR, Calderon J, Taylor GA, Holland JE, Stopp C, White MT, Bellinger DC, Rivkin MJ, Wypij D, Newburger JW. Psychiatric disorders in adolescents with single ventricle congenital heart disease. Pediatrics 2017;e20162241.

ACCEPTED MANUSCRIPT

24. Berghammer MC, Mattsson E, Johansson B, Moons P, Dellborg M. Comparison of participants and non-participants in patient-reported outcome surveys: the case of Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease–International Study. Cardiol Young 2017;27:427-434.

25. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, Eisenmann JC. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. Arch Dis Child 2007;92:509-14.

26. McCrindle, BW, Williams RV, Mitchell PD, Hsu DT, Paridon SM, Atz AM, Li JS, Newburger JW. Relationship of patient and medical characteristics to health status in children and adolescents after the Fontan procedure. Circulation 2006;113:1123-1129.

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10 Figure Legends

Fig. 1. Regional variation in QOL ratings in Fontan patients and ASD/VSD patients. Significant regional differences were not observed in Fontan patients (p=.90, *Mean* QOL North America=76.4±15.7, *Mean* QOL Europe=76.9±17.3, *Mean* QOL Asia=75.4±16.2). Significant regional differences were observed in ASD/VSD patients (p=.01), *Mean* QOL North America=84.1±10.9, *Mean* QOL Europe=80.5±13.3, *Mean* QOL Asia=75.3±16.4).

11 Appendices

None

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Table 1. *Demographic and geographic regional distribution in Fontan patients and ASD/VSD patients.*

	Fontan (n=163)	ASD/VSD (n=242)	*p*-value
Mean Age: Years	27.4±7.6	37.0±14.6	<.001
Sex: Male	85 (52.1%)	97 (40.1%)	.017
Employment Status			.10
Full-time or part-time paid word	98 (61.6%)	168 (69.7%)	
Other	61 (38.4%)	73 (30.3%)	
Marital Status			.001
Married or remarried	33 (20.4%)	87 (36.1%)	
Other	129 (79.6%)	154 (63.9%)	
Ethnical Background			.61
White/Caucasian	112 (70.0%)	168 (71.2%)	
Asian	40 (25.0%	58 (24.6%)	
Black/African-American	4 (2.5%)	2 (0.8%)	
Middle-Eastern/Arabic	3 (1.9%)	3 (1.3%)	
Hispanic/Latino	1 (0.6%)	3 (1.3%	
Other	0 (0.0%)	2 (0.8%)	
Continent			.001
Asia	34 (20.9%)	55 (22.7%)	
India	21 (12.9%)	8 (3.3%)	
Japan	13 (8.0%)	18 (7.4%)	
Taiwan	0 (0.0%)	29 (12.0%)	
Europe	63 (38.7%)	142 (58.7%)	
Belgium	2 (1.2%)	25 (10.3%)	
France	16 (9.8%)	4 (1.7%)	
Italy	1 (0.6%)	10 (4.1%)	
Malta	4 (2.5%)	6 (2.5%)	
Norway	16 (9.8%)	2 (0.8%)	
Sweden	21 (13.0%)	51 (21.1%)	
Switzerland	2 (1.2%)	13 (5.4%)	
The Netherlands	1 (0.6%)	31 (12.8%)	
North America	66 (40.5%)	45 (18.6%)	
Canada	18 (11.0%)	17 (7.0%)	
USA	48 (29.5%)	28 (11.6%)	

Note: Total percentage of patients for each variable are presented in parentheses.

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Table 2. *Medical complications and mood and anxiety disorders in Fontan patients and ASD/VSD patients.*

	Fontan (n=163)	ASD/VSD (n=242)	*p*-value
Medical Complications			
Cardiac surgery	163 (100%)	35 (28.6%)	<.001
Interventional cardiac catheterization	81 (55.1%)	36 (18.7%)	<.001
Congestive heart failure	32 (20.3%)	6 (2.5%)	<.001
Arrhythmia	72 (44.2%)	35 (14.6%)	<.001
Other medical condition	69 (42.3%)	88 (36.8%)	.002
Cardiac device	44 (30.3%)	6 (3.2%)	<.001
Inpatient cardiac admission	85 (55.5%)	42 (18.1%)	<.001
Mood and Anxiety Disorders			
Mood disorder	22 (13.5%)	8 (3.3%)	<.001
Anxiety disorder	18 (11.0%)	7 (2.9%)	<.001
Mood disorder + Anxiety disorder	6 (3.7%)	2 (0.8%)	.001

Note: Total percentage of patients for each variable are presented in parentheses.

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Table 3. *Medical complications and mood and anxiety disorders associated with QOL ratings in Fontan patients and ASD/VSD patients.*

	Fontan (n=163)				ASD/VSD (n=242)			
	B	SE B	β	*p*-value	B	SE B	β	*p*-value
Medical Complications								
Cardiac surgery	-1.45	0.95	-0.12	0.13	1.14	1.88	0.04	0.55
Interventional cardiac catheterization	-0.90	0.65	-0.12	0.17	-3.23	2.28	-0.11	0.16
Congestive heart failure	-3.11	2.28	-0.11	0.18	0.93	3.77	0.02	0.81
Arrhythmia	-3.11	2.93	-0.10	0.29	-1.42	2.69	-0.04	0.60
Other medical condition	1.58	2.83	0.05	0.58	-2.65	1.95	-0.09	0.18
Cardiac device	-1.42	1.67	-0.08	0.40	0.90	3.49	0.02	0.80
Inpatient cardiac admission	-1.50	0.59	-0.23	0.01	-1.38	1.11	-0.09	0.21
Mood and Anxiety Disorders								
Mood disorder	-9.40	3.95	-0.20	0.02	-10.70	5.03	-0.14	0.03
Anxiety disorder	-9.68	4.21	-0.19	0.02	4.83	5.28	0.06	0.36

Note: B = unstandardized beta; SE B = standard error of unstandardized beta; β = standardized beta.

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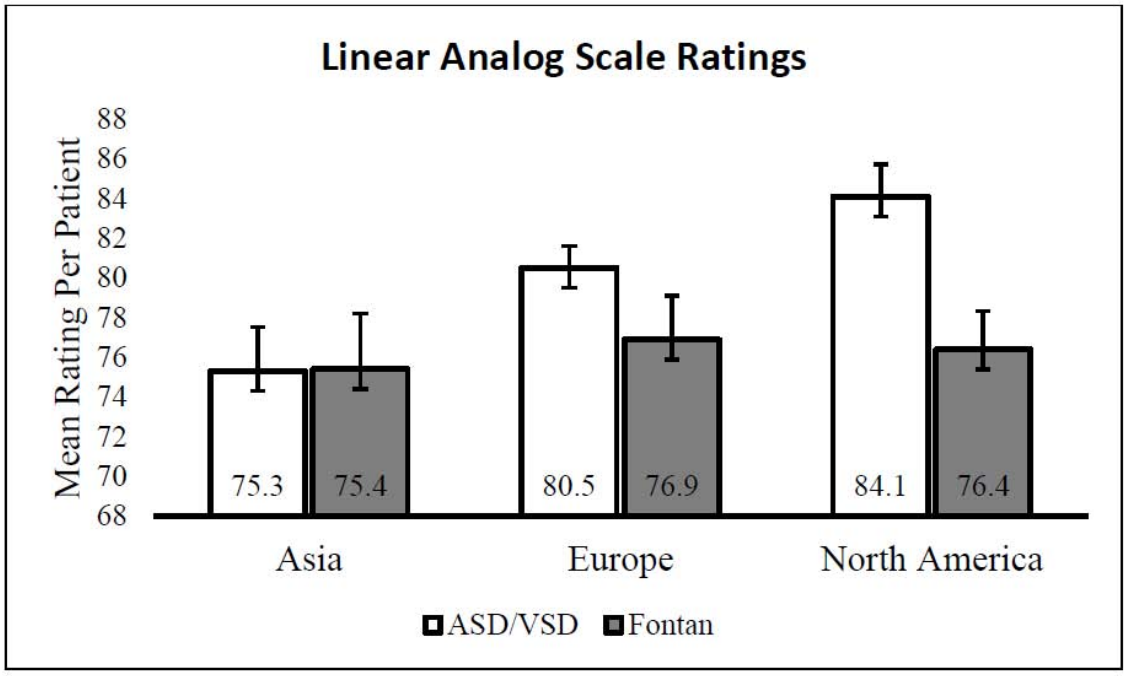

Fig. 1. Regional variation in QOL ratings in Fontan patients and ASD/VSD patients.

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