DR. PHILIP MOONS (Orcid ID : 0000-0002-8609-4516)

Article type : Review Article

Quality of life research in adult patients with congenital heart disease: current status and the way forward

Philip Moons PhD, RN^{1,2,3}, Koen Luyckx PhD^{4,5}

¹ KU Leuven Department of Public Health and Primary Care, Leuven, Belgium

² Institute of Health and Care Sciences, Gothenburg University, Gothenburg, Sweden.

³ Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa.

⁴ School Psychology and Development in Context, KU Leuven - University of Leuven, Leuven, Belgium

⁵ UNIBS, University of the Free State, Bloemfontein, South Africa

Brief title: **Quality of life in congenital heart disease**

This paper is partly based on: *Moons P, Luyckx K. Psychosocial issues in Adult Congenital Heart Disease. In Gatzoulis M, Webb G, Daubeney PEF (Eds.) Diagnosis and management of Adult Congenital Heart Disease (3rd Ed.). (pp281-285) Philadelphia: Elsevier, 2018 (reprinted with permission from Elsevier)*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.14876

This article is protected by copyright. All rights reserved.

It was presented at The Cardiac Patient from Birth to Adulthood symposium in Stockholm from 21-22 February 2019, which was jointly organised by *Acta Paediatrica* and the *Journal of Internal Medicine*.

Address for correspondence: Philip Moons, KU Leuven Department of Public Health and Primary Care, Kapucijnenvoer 35, box 7001, B-3000 Leuven, Belgium; Tel: +32-16-373315; Fax: +32-16-336970, philip.moons@kuleuven.be

ABSTRACT

Over the past four decades, the number of papers on quality of life (QoL) in congenital heart disease (CHD) has grown exponentially. However, firm conclusions have been hard to draw, because conceptual issues occurred and methodological differences prevented direct comparisons of studies. In general, QoL in CHD patients is good and it can be even better than in healthy peers when measured as life satisfaction. When QoL is measured as physical functioning, patients with complex CHD do worse than patients with moderate or mild defects or healthy individuals. APPROACH-IS was a large-scale international project that confirmed international variations in QoL, with Australian patients reporting the best QoL. Poor QoL was predicted by older age, being a job seeker, unemployed or disabled, never having married and those with worse functional status. Perceived illness and religion and spirituality were also significant predictors for QoL. On the other hand, country-specific characteristics and healthcare system factors did not play a significant role in explaining variances in QoL of patients with CHD around the globe. Future studies should rely on a sound conceptual basis, use longitudinal research designs, be conducted in international, multi-centre settings and evaluate interventions that promote patients' QoL.

KEY WORDS: congenital heart disease, heart defects, outcomes, predictors, quality of life

KEY NOTES

- It has been difficult to compare studies on quality of life (QoL) in congenital heart disease (CHD), due to conceptual issues and methodological differences.
- QoL is generally good in CHD and patients can have better QoL than healthy peers when QoL relates to satisfaction with life.
- However, patients with complex CHD have reported worse QoL than patients with moderate or mild defects or healthy individuals with regard to physical functioning

INTRODUCTION

In 1974, the first paper on quality of life (QoL) in congenital heart disease (CHD) was published (1). The article was written by Dr Charlotte Ferencz and was entitled *The quality of life of the adolescent cardiac patients* (1). It was not an empirical study, but rather a scholarly overview on what physicians could do for the adolescent cardiac patient to prevent progressive disease and complications and how they could assist patients to improve their QoL. This seminal article perfectly illustrated the spirit of the times. In the 1970s, the first mid-term successes of cardiac surgery in CHD were observed. As a result, increasingly more children who would have died without operations could now survive into adolescence and adulthood. A new population of adults with congenital heart disease emerged.

Together with the strive for longevity, there was a growing interest in the long-term functioning and QoL of afflicted patients. Indeed, clinicians and researchers were intrigued by the question of how the lives of patients with CHD looked and whether the heart defect had an impact on QoL (2). This increased interest resulted in an exponential growth in QoL studies in CHD since the mid 1970s (2,3) (Figure 1). In the first 40 years after Ferencz's

publication, 234 empirical studies on QoL in children, adolescents and adults with CHD were published (2). These studies were conducted in 35 countries, with the majority performed in the USA (22%), the Netherlands (16%), Germany (13%), the United Kingdom (6%) and Belgium (6%) (2). Based on this information, it cannot be soundly argued that little research on QoL in CHD has been performed. Indeed, numerous QoL studies have been performed and published to date. However, it is important to provide a perspective on what is known and what we still need to know regarding QoL in CHD. Therefore, the aim of the present article was to provide an overview on the current status of QoL research in CHD and to discuss avenues for future research.

The current status of quality-of-life research in adult congenital heart disease

In the past decade, several systematic literature reviews on QoL in (young) adults with CHD have been published. In the first systematic literature review, Fteropoulli et al provided a comprehensive overview of all the relevant quantitative studies on QoL in adults with CHD published until November 2011 (4). These authors found that 20 out of 26 studies reported reduced QoL in patients with CHD in the physical domain. Conversely, 21 of the 24 studies that evaluated psychosocial domains, and four of the six that looked at environmental or occupational domains, found no differences between patients and controls (4). In general, these authors concluded that the available studies produced contradictory findings, possibly resulting from limitations in study methodology.

A second review, performed by Apers et al, expanded the previous review by identifying papers that were published from the end of 2011 until the beginning of 2013 (5). During this period, 11 studies on QoL in young adults with CHD were published and eight compared QoL in patients with CHD to a control group. The studies also reported inconsistent findings: three studies found that QoL was worse in patients with CHD than

control subjects, two studies concluded that QoL was similar and three studies even found that QoL was better in patients with CHD than the control group (5). Apers et al attributed these inconsistent findings to methodological limitations and differences between these studies (5).

The first meta-analysis on QoL in CHD was published in 2015 (6). Schroder et al included studies on adolescents or young adults with mild, moderate or complex CHD and reported QoL as a single index score. The findings were based on comparative data from healthy controls or a reference population (6). This systematic review comprised 18 studies, but six of these were not included in the meta-analysis. The meta-analysis showed that the QoL in adolescents and young adults born with CHD was not reduced when compared to healthy age-matched individuals (6).

Another meta-analysis published in 2015 specifically looked at studies that used the Medical Outcomes Study Short Form-36 (3). Kahr et al conducted analyses for the different levels of complexity of heart defects. They performed their meta-analysis on data from 33 studies (3). This showed that physical functioning and general health perception were significantly lower in patients with moderate or complex heart defects, whereas the scores for patients with mild defects were similar to the controls (3). Given that the majority of the patients with CHD have a mild heart defect, it is understandable that the entire CHD population does not perform worse than the general population, as reported by Schroder's meta-analysis (6).

In 2019, a literature review and meta-analysis of 20 studies was published on health-related QoL in children and young adults who had previously undergone cardiac surgery (7). Patients reported lower scores than healthy controls with regard to generic health-related QoL, with the largest difference seen in physical functioning. However, studies that used the TAPQOL and the KINDL-R tools reported equal or better physical and school functioning

scores in patients compared to controls. This suggests that the results of the studies were a function of the instruments used or of the normative data available. For cardiac-specific QoL, patients with complex heart defects had worse scores in the domains of symptoms, cognitive problems and treatment barriers than individuals with moderate or simple defects (7).

The reviews described above pertained to young adult patients. Contrasting findings have also been observed in studies that were performed on children with CHD (8). A systematic review of children and adolescents following open-heart surgery for CHD revealed that five out of 12 studies reported that their QoL was similar to that of healthy peers, one study found that QoL was better and four of the 12 studies showed a lower QoL in the patients than controls (8).

The systematic reviews and meta-analyses on QoL in CHD illustrate the growth in evidence, but the findings have not always been consistent. It has been shown that the instruments used to measure QoL determined the findings. Hence, the research methodology that was used shaped the findings, which hampered the ability to draw firm conclusions. Indeed, when certain instruments were used, patients were found to report worse QoL than healthy controls. However, when other instruments were employed, patients did just as well as their healthy counterparts. A better QoL in patients compared to healthy counterparts could be explained by a stronger sense of coherence in patients with CHD (9,10). Sense of coherence is a measure of psychological resilience. Growing up with CHD and the stressors associated with it, is believed to strengthen the development of sense of coherence (9). This explains why people do well, despite the adversity of a chronic condition (11).

Determinants of quality of life in CHD

Numerous studies have investigated potential determinants of QoL in afflicted patients. The following correlates of poorer QoL among adults with CHD have been identified: lower academic performance and education (12,13), lower employment rates (13), fewer daily

activities (14), worse functional status (15), lower exercise capacity (14), lower social support (12,16), cardiac surgery (12,16), being given an implantable cardioverter defibrillator (17), physical limitations (12) and a distressed personality type (18). Inconsistent findings were observed regarding the relationship between QoL and age (12,13,16,19), sex (12,13,16), medication (12,16), disease severity (12,13,16) and the severity of residual lesions (12,16). Finally, QoL has been reported to be unrelated to CHD subtypes (12), cyanosis (16), personal resources (16) and the family environment (16)

However, comparisons between these studies have been hampered, because some studies used multivariable analyses, adjusting for confounding factors, whereas other studies only reported univariate analyses. Furthermore, most studies only evaluated the role of demographic and medical factors in predicting QoL. However, there has been a set of relatively new factors that have been reported to have predictive value for QoL in CHD, such as a sense of coherence (10,20,21), general self-efficacy (22), empowerment (23), how the patient perceives their illness (24), personality (25,26), parental support (27-29) and loneliness (29). These novel predictors of a psychological or contextual nature should be included in future studies, in order to capture the entire spectrum of variations in QoL.

Is quality of life the ultimate outcome?

Most QoL studies that have been published to date have used a cross-sectional research design. Such a design allows researchers to explore associations between variables, but does not allow them to examine the direction of effects linking QoL to other variables of interest. In order to do so, longitudinal study designs and the use of cross-lagged path analysis are required (30). Only a few QoL studies in CHD have used a longitudinal design and employed cross-lagged analyses (28,29). These studies showed that depressive symptoms, loneliness, sense of coherence, perceived health and parental support predicted relative changes in QoL

over time, whereas QoL in itself did not predict relative changes in any of these previous variables (28,29). Hence, QoL may be seen as an ultimate outcome parameter in patients with CHD. These observations indirectly confirm the conceptual model of Wilson and Cleary (31). This model describes how individual, environmental and clinical factors have an impact on QoL. In this model, QoL is proposed as the ultimate outcome (31). Although there is mounting evidence to support this model, it has not been tested on CHD patients in its entirety. Therefore, we suggest that more longitudinal studies need to be conducted in patients with CHD to evaluate the direction of the effect between variables of the model. Subsequently, the validity of the Wilson and Cleary model should be tested on CHD patients.

Conceptual and methodological rigour

Irrespective of the large amount of QoL research over the past 40 years, substantial conceptual and methodological problems have been identified. Bratt and Moons reviewed all 234 QoL studies that were published between 1974 and 2014 and looked for temporal trends in the conceptual and methodological rigor by applying 10 review criteria that reflected the quality of the QoL studies (2). Temporal improvements were observed, mainly because more papers with higher quality scores had been published over the previous 10 years (Figure 2). Despite this upward trend, the majority of the papers still had a low quality score. Indeed, during 2005–2014, 52.4% still failed to meet any of the quality criteria (2). This means that major weaknesses in methodological rigour were present in published QoL research. It has been suggested that the scientific community should pay more attention to the conceptual and methodological aspects of QoL and, by doing so, increase the quality of QoL studies (2). More specifically, several recommendations have been made about future QoL research. Authors are required to provide the definition of QoL that they have used in their study and to explicitly state the domains that they have measured as components of QoL. They are also

recommended to give the reasons for choosing the instruments they used or state whether they measured overall QoL or health-related QoL. Finally, they are expected to explicitly state the indicators and determinants of QoL that they have measured in their study (32).

Although there are eight different conceptual approaches to QoL possible (33), two approaches are often used in CHD. Most QoL studies measure CHD by using the normal life approach (2). Defining QoL in terms of normal life results in measuring an individual's functional problems and refers predominantly to the patient's health status (33). This type of conceptualisation is very often referred to as health-related quality of life. Another conceptual approach that has received increasing attention is assessing QoL as satisfaction with life (33), which refers to a subjective appraisal of an individual's personal life. Overall satisfaction with life can be considered to be an indicator of quality of life, because the respondent indicates how satisfied they are with their life as a whole. Because satisfaction with life is a concept that emerged from the field of positive psychology, it focuses on strengths and talents as opposed to shortcomings and weaknesses. Consequently, satisfaction with life corresponds to overall quality of life and is not limited to health-related quality of life (33).

It is obvious that the conceptualisation and operationalisation of QoL will have an impact on the findings of the studies. When QoL has been measured from a functional approach, it is not surprising that patients with CHD, especially the ones with complex heart defects, were reported to be doing worse than healthy controls (3). However, when QoL was measured from a more holistic perspective, it is understandable that patients valued their life as highly as healthy individuals and, therefore, they were equally or sometimes even more satisfied with their life (34).

Geographical variations

A fascinating observation by Kahr et al in their meta-analysis was that the QoL of patients from the Netherlands and Switzerland was better than that of patients from the USA and Canada (3). Country of residence clearly moderated the relationship between disease complexity and QoL. However, it can be questioned if the geographical variations represented genuine differences across the countries or if they were a function of methodological differences in the respective studies. To address this issue, international studies employing a uniform research methodology are vital.

APPROACH-IS

One international study that is worth highlighting in this respect is the Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease - International Study (APPROACH-IS) (35). The aims of APPROACH-IS were two-fold. The first was to investigate differences in patient-reported outcome, including QoL, in adults with CHD who were living in different areas of the world. The second was to gain insights into how international differences could be understood (35). Overall, 4,028 patients from 24 centres in 15 countries across five continents were included (36). Standardised self-report questionnaires were used to measure primary and secondary outcomes. The primary outcomes were four patient-reported domains. The first was perceived health status using the 12-item Short Form Health Survey (37) and the EuroQoL-5D Visual Analog Scale (38). The second was psychological functioning using the Hospital Anxiety and Depression Scale (39). The third was health behaviours, such as dental hygiene, sports participation, the use of alcohol, tobacco, and, or, drugs using the Health Behavior Scale–Congenital Heart Disease (40). The final outcome domain was quality of life using a Linear Analog Scale (34) and the

Satisfaction With Life Scale (41). This means that APPROACH-IS measured QoL from a holistic rather than a functional perspective. The secondary outcomes were potential explanatory variables and included sense of coherence, which was measured using the 13-item Orientation to Life Questionnaire (42), and illness perceptions, which was assessed with the Brief Illness Perception Questionnaire (43). These questionnaires were chosen based on their psychometric properties, their extensive use in previous studies and because they were available in different languages. Socio-demographic data were collected by self-reports and information on medical history was retrieved by chart reviews. Details on the methodology of APPROACH-IS have been provided in a methods paper (35) and numerous papers have described findings obtained from this global sample (36,44-52) or from patients from specific countries or regions (22,53-60).

Quality of life and inter-country variations

APPROACH-IS reported that the median QoL score was 80.0 on the linear analogue scale ranging from 0-100 (36). There were large variations in QoL scores, with over 90% of patients reporting a score of more than 50. Patients from Australia had the highest QoL (82.1) and patients from Japan had the lowest (71.6), representing a substantial gap of 10.5 points (Figure 3). Overall, four countries had a median score of at least 80, namely Australia, Switzerland, the USA and Malta. All the other countries, with the exception of Japan, had a median QoL score of at least 75 (36).

Patient characteristics as predictors of quality of life

A number of factors were associated with worse QoL in this large international sample of patients with CHD. These were: older age, job seeking, being unemployed or disabled, never having been married and higher New York Heart Association functional classes, indicating

worse functional status (36, 46). These factors explained 20% of the variance of QoL, indicating that there was still a large portion of the variance that could not be explained. APPROACH-IS reported that sex, educational level and the complexity of the heart defect were not associated with QoL (36,46). The finding that disease complexity did not play a role in predicting QoL could be explained by the fact that we measured QoL from a holistic point of view, instead of a merely functional perspective. We also conducted multivariable analyses by including functional class as one of the covariates. Indeed, univariate analyses showed differences in QoL in mild, moderate and complex heart defects. However, when disease complexity was adjusted for New York Heart Association functional class it was no longer predictive.

Typically, predictors of QoL and other patient-reported outcomes are investigated using linear statistical approaches. Such techniques assume that the relationships between the predictors and QoL is linear. However, using segmented regression analysis, we were able to demonstrate that QoL was related to age in a non-linear fashion (61). Segmented regression analysis is a technique that allows researchers to identify the breakpoints in age at which QoL starts to deteriorate, improve or stabilise. We conducted these analyses for the three categories of disease complexity: mild, moderate and complex heart defects. We found that the age breakpoints for QoL for mild, moderate and complex CHD were at 51.8, 43.0 and 32.8 years, respectively. Before the breakpoint, the QoL scores decreased in patients with mild and moderate disease and QoL remained stable in both groups after the breakpoint. In patients with complex CHD, the QoL score was stable before the breakpoint, but significantly decreased after that point. Therefore, we concluded that patients with complex CHD were vulnerable with regards to deteriorating QoL, particularly beyond their third decade of life (61).

Relationships with illness perceptions

Illness perceptions are a cognitive framework that afflicted individuals construct to make sense of their illness (43). Therefore, it is believed that illness perceptions can impact patients' QoL. Indeed, APPROACH-IS showed that patients with a poorer QoL perceived their illness as having more consequences, had weaker perceptions of personal control and were less likely to believe that their treatment could control their illness. They also perceived more symptoms, had a less coherent understanding of their illness and experienced more negative emotions (44). Overall, illness perceptions explained 16% of the variance in QoL (44).

Relationships with religion and spirituality

Religion and spirituality are dimensions of health that are often overlooked or even completely neglected (62), but they can provide resources for internal strength and resilience and may have an impact on promoting good QoL. Since APPROACH-IS included patients from different countries and religions, the study allowed us to investigate if being religious or spiritual was an independent predictor of QoL. We were also able to explore whether the individual level of importance of religion or spirituality, in other words, the central role that religion or spirituality played in a person's life, was an independent predictor for QoL (49). Overall, 49% of patients considered themselves to be religious or spiritual. After adjusting for patient characteristics and country differences, being religious or spiritual and considering religion or spirituality as important in a person's life was positively associated with QoL (49). These findings suggest that QoL studies should include religion or spirituality when assessing potential predictors of QoL.

Relationships with country-specific and healthcare system factors

Even when patient characteristics and illness perceptions were combined, two-thirds of the variance of QoL remain unexplained (44). In addition to identify more patient characteristics that could be of relevance, it is worthwhile to explore country-specific features and healthcare system factors that may explain variances of QoL above and beyond patient qualities. APPROACH-IS investigated the roles that the level of national happiness (36), cultural dimensions (36), standard of living (46) and healthcare system factors (46,60) played in predicting QoL. These analyses demonstrated that QoL was not related to any of these country-specific or healthcare system factors (36,46, 60). This current knowledge means that there have been no factors identified beyond patient characteristics that explain QoL in adults with CHD.

The way forward

The increasing number of empirical studies on QoL in CHD that have been published over the past four decades has contributed significantly to the growing insights into the impact of CHD on patients' lives. However, as discussed above, the current body of knowledge has been hampered by some limitations. Future studies need to address these limitations, in order to allow the CHD scientific community to expand their knowledge of QoL in affected patients.

First, it is vital that researchers address the substantial conceptual and methodological issues in existing QoL studies, so that they can provide a better conceptual basis for their work. Indeed, there is extensive room for improvements. The scientific community should pay more attention to conceptual and methodological papers dealing with QoL, because they may substantially advance the calibre and impact of QoL studies (2).

When they plan future QoL studies, researchers should take the proposed requirements that have been described above into consideration (2,32).

Second, most studies have used a cross-sectional design, which makes it impossible draw conclusions on temporal sequences and the direction of effects (5). Longitudinal research is required to examine how QoL changes over time and to assess the direction of effects between QoL and possible determinants and concomitants in adults with CHD. Detailed information on the changes in, and stability of, QoL can help to identify vulnerable groups of patients, for example those with a consistently low QoL over time (5).

Third, international multicentre studies that use uniform methodology, are needed (5). Such international studies would ensure the generalisability of the findings, enable researchers and health professionals to make valid comparisons and allow researchers to investigate the role of system factors in explaining QoL. APPROACH-IS was the first study of this kind and provided invaluable insights. However, it also raised more questions and more studies of this calibre are required. The APPROACH-IS II study is currently in the planning phase and more than 70 centres from over 30 countries have signed up to participate in this new international, multicentre project.

Fourth, a critical step in future research is to understand how QoL can be optimised in patients with CHD through the implementation of interventions that target modifiable determinants (5). For instance, based on the current evidence in adolescents with CHD, sense of coherence seems to be a key factor in promoting QoL (10,20,21). However, there have not been any studies that have examined interventions that have strengthened sense of coherence and, consequently, improved QoL in patients with CHD (5). Such interventions should focus on empowering patients and enhancing their feelings of comprehensibility, manageability and meaningfulness. They can do this by providing

information, making patients aware of available resources, and supporting patients to play an active role in their care (9,23,63).

CONCLUSION

Over the past four decades, a large number of QoL studies have been published and the overall conclusion is that the QoL of adults with CHD is good. People with CHD can even have a better QoL than their healthy peers if QoL is measured holistically in terms of satisfaction with life. When QoL is measured in terms of physical functioning, patients with complex heart defects tend to do worse than patients with moderate or mild defects and healthy individuals. Studies have reported international variations in QoL when they have used uniform methodology. For example, patients from Australia were reported to have the best QoL and patients from Japan had the worst QoL. Poor QoL was independently predicted by older age, job seeking, being unemployed or disabled, never having been married and worse functional status. Illness perceptions and religion or spirituality were significant predictors for QoL, above and beyond patient characteristics. On the other hand, factors such as national happiness, cultural dimensions, standard of living and the characteristics and performance of healthcare systems did not play a significant role in explaining variance in QoL of patients with CHD around the globe. Future studies should rely on a sound conceptual basis, use longitudinal research designs, be conducted in international, multicentre settings and evaluate interventions that promote patients' QoL.

ABBREVIATIONS

CHD, congenital heart disease; QoL, quality of life; APPROACH-IS, Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease - International Study

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare

FINANCE

This study did not receive any specific funding

References

1. Ferencz C. The quality of life of the adolescent cardiac patient. *Postgrad Med* 1974; 56: 67-73.
2. 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.
3. 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.
4. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young* 2013; 23: 473-85.
5. Apers S, Luyckx K, Moons P. Quality of life in adult congenital heart disease: what do we already know and what do we still need to know? *Curr Cardiol Rep* 2013; 15: 407.
6. Schroder M, Boisen KA, Reimers J, Teilmann G, Brok J. Quality of life in adolescents and young adults with CHD is not reduced: a systematic review and meta-analysis. *Cardiol Young* 2016; 26: 415-25.

7. 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.
8. Latal B, Helfricht S, Fischer JE, Bauersfeld U, Landolt MA. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: a systematic review. *BMCPediatr* 2009; 9: 6.
9. Moons P, Norekval TM. Is sense of coherence a pathway for improving the quality of life of patients who grow up with chronic diseases? A hypothesis. *Eur J Cardiovasc Nurs* 2006; 5: 16-20.
10. Apers S, Moons P, Goossens E, Luyckx K, Gewillig M, Bogaerts K, et al. 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.
11. Moons P, Norekval TM. Why some people do well and others don't. The role of sense of coherence in disease adaptation. *Eur J Cardiovasc Nurs* 2018; 17: 672-4.
12. Teixeira FM, Coelho RM, Proenca C, Silva AM, Vieira D, Vaz C, et al. Quality of life experienced by adolescents and young adults with congenital heart disease. *Pediatr Cardiol* 2011; 32: 1132-8.
13. Vigl M, Niggemeyer E, Hager A, Schwedler G, Kropf S, Bauer U. The importance of socio-demographic factors for the quality of life of adults with congenital heart disease. *Qual Life Res* 2011; 20: 169-77.
14. Muller J, Hess J, Hager A. Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life. *Clin Res Cardiol* 2012; 101: 55-61.

- Accepted Article
15. Overgaard D, Schrader AM, Lisby KH, King C, Christensen RF, Jensen HF, et al. Patient-reported outcomes in adult survivors with single-ventricle physiology. *Cardiology* 2011; 120: 36-42.
 16. Silva AM, Vaz C, Areias ME, Vieira D, Proenca C, Viana V, et al. Quality of life of patients with congenital heart diseases. *Cardiol Young* 2011; 21: 670-6.
 17. Opic P, Utens EM, Moons P, Theuns DA, van Dijk AP, Hoendermis ES, et al. Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults with Tetralogy of Fallot. *Clin Res Cardiol* 2012; 101: 509-19.
 18. Schoormans D, Mulder BJ, van Melle JP, Pieper EG, van Dijk AP, Sieswerda GJ, et al. Patients with a congenital heart defect and type D personality feel functionally more impaired, report a poorer health status and quality of life, but use less healthcare. *Eur J Cardiovasc Nurs* 2012; 11: 349-55.
 19. Cotts T, Malviya S, Goldberg C. Quality of life and perceived health status in adults with congenitally corrected transposition of the great arteries. *J Thorac Cardiovasc Surg* 2012; 143: 885-90.
 20. Neuner B, Busch MA, Singer S, Moons P, Wellmann J, Bauer U, et al. Sense of Coherence as a Predictor of Quality of Life in Adolescents With Congenital Heart Defects: A Register-Based 1-Year Follow-Up Study. *J Dev Behav Pediatr* 2011; 32: 316-27.
 21. Muller J, Hess J, Hager A. Sense of coherence, rather than exercise capacity, is the stronger predictor to obtain health-related quality of life in adults with congenital heart disease. *Eur J Prev Cardiol* 2014; 21: 949-55.
 22. Thomet C, Moons P, Schwerzmann M, Apers S, Luyckx K, Oechslin EN, et al. Self-efficacy as a predictor of patient-reported outcomes in adults with congenital heart disease. *Eur J Cardiovasc Nurs* 2018; 17: 619-26.

- Accepted Article
23. Acuna Mora M, Sparud-Lundin C, Burstrom A, Hanseus K, Rydberg A, Moons P, et al. Patient empowerment and its correlates in young persons with congenital heart disease. *Eur J Cardiovasc Nurs* 2019; doi 10.1177/1474515119835434.
 24. Schoormans D, Mulder BJ, van Melle JP, Pieper PG, van Dijk AP, Sieswerda GT, et al. Illness perceptions of adults with congenital heart disease and their predictive value for quality of life two years later. *Eur J Cardiovasc Nurs* 2014; 13: 86-94.
 25. Rassart J, Luyckx K, Goossens E, Apers S, Klimstra TA, Moons P. Personality traits, quality of life and perceived health in adolescents with congenital heart disease. *Psychol Health* 2013; 28: 319-35.
 26. Rassart J, Luyckx K, Goossens E, Oris L, Apers S, Moons P, et al. A Big Five Personality Typology in Adolescents with Congenital Heart Disease: Prospective Associations with Psychosocial Functioning and Perceived Health. *Int J Behav Med* 2016; 23: 310-8.
 27. Luyckx K, Goossens E, Missotten L, Moons P. Adolescents with congenital heart disease: the importance of perceived parenting for psychosocial and health outcomes. *J Dev Behav Pediatr* 2011; 32: 651-9.
 28. Luyckx K, Missotten L, Goossens E, Moons P, i-Detach Investigators. Individual and contextual determinants of quality of life in adolescents with congenital heart disease. *J Adolesc Health* 2012; 51: 122-8.
 29. Luyckx K, Goossens E, Rassart J, Apers S, Vanhalst J, Moons P. Parental support, internalizing symptoms, perceived health status, and quality of life in adolescents with congenital heart disease: influences and reciprocal effects. *J Behav Med* 2014; 37: 145-55.
 30. Apers S, Luyckx K, Moons P. Is quality of life the ultimate outcome parameter? *Eur J Cardiovasc Nurs* 2013; 12: 502-4.

31. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 1995; 273: 59-65.
32. Moons P, Jaarsma T, Norekval TM. Requirements for quality-of-life reports. *Eur J Cardiovasc Nurs* 2010; 9: 141-3.
33. 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.
34. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, 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.
35. Apers S, Kovacs AH, Luyckx K, Alday L, Berghammer M, Budts W, 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.
36. Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, 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.
37. Ware JE, Kosinski M, Turner-Bowker DM, Sundaram M, Gandek B, Maruish ME. User's Manual for the SF-12v2 Health Survey Second Edition: *QualityMetric, Incorporated*, 2009.
38. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199-208.
39. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.

40. Goossens E, Luyckx K, Mommen N, Gewillig M, Budts W, Zupancic N, et al. 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.
41. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction with Life Scale. *J Pers Assess* 1985; 49: 71-5.
42. Antonovsky A. The structure and properties of the sense of coherence scale. *Soc Sci Med* 1993; 36: 725-33.
43. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006; 60: 631-7.
44. Rassart J, Apers S, Kovacs AH, Moons P, Thomet C, Budts W, et al. Illness perceptions in adult congenital heart disease: A multi-center international study. *Int J Cardiol* 2017; 244: 130-8.
45. Fogleman ND, Apers S, Moons P, Morrison S, Wittekind SG, Tomlin M, et al. Regional variation in quality of life in patients with a Fontan circulation: A multinational perspective. *Am Heart J* 2017; 193: 55-62.
46. Moons P, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, 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.
47. Holbein CE, Fogleman ND, Hommel K, Apers S, Rassart J, Moons P, 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.
48. Ko JM, White KS, Kovacs AH, Tecson KM, Apers S, Luyckx K, et al. Physical Activity-Related Drivers of Perceived Health Status in Adults With Congenital Heart Disease. *Am J Cardiol* 2018; 122: 1437-42.

49. Moons P, Luyckx K, Dezutter J, Kovacs AH, Thomet C, Budts W, et al. Religion and spirituality as predictors of patient-reported outcomes in adults with congenital heart disease around the globe. *Int J Cardiol* 2019; 274: 93-9.
50. Sluman MA, Apers S, Sluiter JK, Nieuwenhuijsen K, Moons P, Luyckx K, et al. Education as important predictor for successful employment in adults with congenital heart disease worldwide. *Congenit Heart Dis* 2019: doi 10.1111/chd.12747.
51. Larsson L, Johansson B, Sandberg C, Apers S, Kovacs AH, Luyckx K, et al. Geographical variation and predictors of physical activity level in adults with congenital heart disease. *Int J Cardiol Heart Vasc* 2019; 22: 20-5.
52. Holbein CE, Veldtman GR, Moons P, Kovacs AH, Luyckx K, Apers S, et al. Perceived Health Mediates Effects of Physical Activity on Quality of Life in Patients With a Fontan Circulation. *Am J Cardiol* 2019: doi 10.1016/j.amjcard.2019.03.039.
53. 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: 427-34.
54. Caruana M, Apers S, Kovacs AH, Luyckx K, Thomet C, Budts W, et al. Red Flags for Maltese Adults with Congenital Heart Disease: Poorer Dental Care and Less Sports Participation Compared to Other European Patients-An APPROACH-IS Substudy. *Pediatr Cardiol* 2017; 38: 965-73.
55. Eaton SL, Wang QF, Menahem S. Determinants of quality of life in adults with CHD: an Australian cohort. *Cardiol Young* 2017; 27: 1571-6.
56. Bay A, Dellborg M, Berghammer M, Sandberg C, Engstrom G, Moons P, et al. Patient reported outcomes are associated with physical activity level in adults with congenital heart disease. *Int J Cardiol* 2017; 243: 174-9.

57. Caruana M, Moons P, Kovacs A, Luyckx K, Thomet C, Budts W, et al. Quality of life in Maltese Adults with Congenital Heart Disease: a Second Look – An APPROACH-IS Substudy. *International Cardiovascular Forum Journal* 2017; 12: 18-23.
58. Oris L, Luyckx K, Rassart J, Goubert L, Goossens E, Apers S, et al. Illness Identity in Adults with a Chronic Illness. *J Clin Psychol Med Settings* 2018; 25: 429-40.
59. Van Bulck L, Goossens E, Luyckx K, Oris L, Apers S, Moons P. Illness Identity: A Novel Predictor for Healthcare Use in Adults With Congenital Heart Disease. *Journal of the American Heart Association* 2018; 7: e008723.
60. Van Bulck L, Luyckx K, Goossens E, Apers S, Kovacs AH, Thomet C, et al. Patient-reported outcomes of adults with congenital heart disease from eight European countries: scrutinising the association with healthcare system performance. *Eur J Cardiovasc Nurs* 2019: doi 10.1177/1474515119834484.
61. Moons P, Apers S, Luyckx K, Kovacs AH, Thomet C, Budts W, et al. Abstract 14623: Age and Quality of Life in Adults With Congenital Heart Disease Worldwide: Evidence for a Non-Linear Relationship. *Circulation* 2018; 138: A14623-A.
62. VanderWeele TJ, Balboni TA, Koh HK. Health and Spirituality. *JAMA* 2017; 318: 519-20.
63. Acuña Mora M, Sparud-Lundin C, Bratt E-L, Moons P. Person-centred transition programme to empower adolescents with congenital heart disease in the transition to adulthood: a study protocol for a hybrid randomised controlled trial (STEPSTONES project). *BMJ Open* 2017; 7: e014593.

Figure 1. Number of papers on quality of life in patients with congenital heart disease published per year between 1974 and 2014.

Adapted version reprinted from Bratt and Moons (2) with permission from Elsevier.

Figure 2. Temporal trends in conceptual and methodological rigor of quality of life studies in congenital heart disease

Adapted version reprinted from Bratt and Moons (2) with permission from Elsevier.

Figure 3. Distribution of quality of life (heat map) in adults with congenital heart disease, ranked on the empirical Bayes estimate

Country	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	EB estimate quality of life (95%CI)
Australia	0.0%	0.0%	0.0%	3.0%	3.0%	1.5%	12.9%	20.5%	33.3%	25.8%	82.1 (79.6;84.6)
Switzerland	0.0%	0.4%	0.4%	2.2%	4.4%	6.6%	11.0%	16.9%	31.6%	26.5%	81.4 (79.5;83.2)
USA	0.1%	1.1%	1.5%	1.9%	4.8%	3.7%	10.5%	22.5%	28.2%	25.7%	80.4 (79.3;81.6)
Malta	0.0%	0.9%	0.0%	0.0%	4.3%	5.1%	11.1%	32.5%	34.2%	12.0%	80.1 (77.5;82.8)
the Netherlands	0.4%	0.0%	0.8%	0.4%	0.4%	2.4%	17.3%	37.3%	28.5%	12.4%	79.9 (78.0;81.8)
Sweden	0.9%	0.9%	1.5%	2.6%	3.1%	4.6%	12.6%	20.9%	29.2%	23.7%	79.4 (78.0;80.9)
Argentina	1.2%	0.0%	0.6%	0.0%	3.5%	6.4%	15.0%	30.1%	35.3%	8.1%	79.3 (77.1;81.6)
Italy	0.0%	0.0%	0.0%	3.2%	6.3%	3.2%	12.7%	30.2%	30.2%	14.3%	79.2 (75.9;82.5)
France	0.0%	0.0%	0.0%	2.1%	6.3%	5.3%	17.9%	25.3%	25.3%	17.9%	78.6 (75.8;81.5)
Belgium	0.0%	0.7%	1.1%	1.5%	4.4%	5.5%	16.5%	33.5%	28.3%	8.5%	77.0 (75.2;78.9)
India	1.5%	0.0%	1.0%	2.5%	6.1%	10.6%	19.2%	21.2%	17.7%	20.2%	76.9 (74.8;79.0)
Norway	0.0%	1.2%	1.2%	4.0%	5.2%	6.4%	16.8%	24.3%	23.7%	17.3%	76.9 (74.6;79.1)
Canada	0.8%	0.2%	1.4%	1.6%	4.3%	8.4%	19.9%	28.3%	23.8%	11.5%	76.1 (74.7;77.5)
Taiwan	0.0%	0.4%	1.6%	0.8%	6.8%	9.6%	18.1%	31.3%	24.9%	6.4%	75.6 (73.7;77.5)
Japan	1.6%	2.4%	4.0%	4.0%	8.3%	7.1%	15.4%	24.1%	21.3%	11.9%	71.6 (69.7;73.5)
Total sample	0.5%	0.7%	1.3%	1.9%	4.6%	5.8%	14.9%	25.8%	27.3%	17.4%	Median quality of life (IQR) 80.0 (20.0)

EB estimate: Empirical Bayes estimate; IQR: interquartile range.

Adapted version reprinted from Apers et al (36) with permission from Elsevier