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The "Well-being paradox" revisited: Quality of life and psychosocial long-term outcomes in over 4,000 adults with congenital heart disease

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Abstract

Objective: The present cross-sectional study investigated quality of life (QOL) in a large cohort of German adults with congenital heart disease (ACHD) in association with sociodemographic and clinical variables.

Methods: Patient reported outcome measures on demographic and clinical variables were retrospectively analysed in a representative sample of 4,015 adults with various forms of CHD (41.8 ± 17.2 years; 46.5% female). QOL was assessed using the EQ-5D-5L. Associations of QOL with patient reported clinical and sociodemographic variables were quantified using multiple regression analysis and multiple ordinal logit models.

Results: Overall, ACHD patients reported a good QOL comparable to German population norms. The most frequently reported complaints occurred in the dimensions pain/discomfort and anxiety/depression. QOL differed significantly within ACHD subgroups, with patients affected by pre-tricuspid shunt lesions indicating the most significant impairments. Older age, female sex, medication intake and the presence of comorbidities, were associated with significant reductions in QOL. CHD severity was positively associated with QOL.

Conclusion: Current findings temper widely held assumptions among clinicians and confirm that ACHD experience a generally good QOL. However, specific subgroups may require additional support to cope with disease-related challenges. The negative correlation of QOL with age is especially alarming as the population of ACHD is expected to grow older in the future.

Keywords: *adults with congenital heart disease; psychological situation; quality of life; prevention; EQ5D*

Strenghts and Limitations

- First study of its kind exploring quality of life (QOL) among 4,015 patients with different medical and sociodemographic backgrounds.
- Uniform conceptualization of QOL based on EQ-5D-5L, which is a highly reliable and valid outcome measure within the cardiovascular area.
- Present findings help clinicians to identify specific subsets of patients who require extra psychological support and therefore constitute a major step in paving the way towards integrative cardiac care.
- Causal inferences are not possible due to the cross-sectional design of this study.
- Ambiguous findings open new avenues for future research in understanding the construction of self-rated health despite or as a consequence of CHD.

Introduction

Although most patients with congenital heart disease (CHD) survive into adulthood, many of them are not cured and need to adapt to their chronic medical condition throughout their lives [1]. Besides symptoms related to their heart disease, lifelong psychosocial impairments may seriously impact the patients´ perceived quality of life (QOL) [2]. While clinical research traditionally focused on objective medical outcomes, the relevance of QOL is increasingly recognized in the evaluation of care for adults with congenital heart disease (ACHD) [3].

Research on QOL in ACHD is still relatively scarce and not conclusive. Empirical findings indicate that QOL among ACHD is compromised by sociodemographic factors (unemployment, older age, single status), psychological features (negative illness perceptions, distressed personality) and medical characteristics (e.g. hospitalization, worse functional status). QOL has been found to be positively associated with higher socioeconomic and educational status, stronger social support, better functional class, better knowledge of CHD, stronger sense of coherence as well as the absence of cardiac surgery. Existing findings are inconsistent regarding cardiovascular status, medication, age, and gender, although these variables appeared to be the most frequently investigated determinants [4].

These inconsistent results of existing research on QOL in ACHD can be attributed to a lack of a clear conceptual background, inconsistent methods and insufficient sample sizes [4]. Additionally, the high heterogeneity of ACHD constitutes a substantial confounding factor due to their great anatomical and clinical disease complexity. Most studies on QOL in ACHD focused on specific subgroups of patients which limits their informational value. Consequently, clinical parameters were not sufficiently examined to explain potential differences in QOL by the underlying diagnosis or severity of CHD. Although a recent review attests temporal qualitative improvements in QOL studies over the last decades, the current research situation still fails to meet scientific quality criteria [5].

The present study aimed to assess QOL within a large sample of ACHD in Germany and examine potential determinants of QOL in terms of patient reported sociodemographic and medical characteristics. Identifying determinants of QOL along with special needs of ACHD could advance the improvement of health care for this growing patient population.

Methods

Population

The study was conducted at the Dpt. of Congenital Heart Disease and Pediatric Cardiology at the German Heart Center Munich, Technical University Munich, under the approval of the Ethics Committee of the contributing centers (TU Munich 157/16S). Guidelines on good clinical practice and data protection guidelines were followed. As part of the ongoing cross-sectional VEMAH research

project (engl. "Medical Care Situation of ACHD") it constitutes the largest ever attempt to comprehensively assess the health care situation of ACHD in Germany. Inclusion criteria were: (1) confirmed diagnosis of CHD, (2) participant age 18 years and older, (3) necessary physical, cognitive and language capabilities to complete self-report questionnaires, (4) German speaking. No patients were asked for input in the creation of this research.

Measures

Patients completed a questionnaire either in person, online or by mail to maximize response. Data collection took place between 2016 and 2019. QOL was measured using the generic questionnaire EQ-5D-5L[6].

I. *Demographic and clinical information*

Sociodemographic and medical information was obtained by a self-devised questionnaire. Medical variables included leading CHD, medication, presence of cyanosis, (non-) cardiac comorbidities and hereditary diseases. Following the recommendations of the American College of Cardiology, patients were divided into three severity groups based on their CHD diagnosis (ACC) [7].

II. *Quality of Life (EQ-5D-5L)*

QOL was measured using the updated five-level version of the EQ-5D [6] which provides a simple, generic measure of a patient's perceived health status. The EQ-5D-5L consists of a descriptive system questionnaire and a visual analogue scale (VAS). The descriptive system compromises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each patient was asked to indicate his perceived impairments on a 5-point Likert scale ranging from "no problems" to "extreme problems/unable". Responses were converted into a single weighted index score (EQ-5D index) which indicates how good or poorthe respondent´s health status is based on existing population norms. A value set for the EQ-5D-5L, based on a representative sample of the German population, has recently been developed [8]. The VAS indicates a patient's overall health state on the day of the questionnaire completion. It is a scale which ranges from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine") and provides a quantitative measure of a patient's perceived health. The EQ-5D-5L proved to be a reliable and valid method for measuring QOL in cardiovascular populations (Cronbach's alpha = 0.856) [9].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 (IBM, Armond, New York, United States). Descriptive measures were calculated for sample characteristics, including patient reported sociodemographic and medical variables (absolute and relative frequencies, mean and standard deviations). The relationships between CHD diagnosis groups and EQ-5D-index values, including the underlying dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression were

analysed. The comparison of ordinally scaled values was based on cumulative frequencies representing the relative proportion of patients with moderate to severe symptoms on the specific dimensions. Kruskal-Wallis-tests were applied to reveal significant differences between EQ-5D-dimensions and metric index values. Furthermore, the relationship between both EQ-5D VAS scores and dedicated index values was analysed with respect to various patient characteristics. Multiple regression models using Ordinary least squares (OLS)-estimates were calculated, while bivariate Pearson-coefficients were used to analyse the correlation between VAS and index scores. Finally, multiple ordinal logit models were applied to identify significant predictors of the respective QOL dimensions.

Patient and Public Involvement

Neither patients nor the public were involved in the design and conduct of this research. The methodology of this research was adapted in multidisciplinary collaboration.

Results

Sample characteristics

A total of 4,015 patients was analysed (46.5% female) (***Table 1).*** The mean age of ACHD was 41.8 ± 17.2 [18-97] years. Patients were subclassified according to the underlying CHD into six main groups, consisting of complex CHD (n=581); pre-tricuspid shunts (n=621); post-tricuspid shunts (n=406); right heart or pulmonary artery anomalies (n=526); left heart or aortic anomalies (n=898); and miscellaneous CHD (n=602). 15.4 % of patients (n=602) presented with cyanosis. The severity of CHD was determined according to the Warnes classification system as simple (n=1,722, 62.0%), intermediate (n=650, 23.4%) or severe (n=406, 14.6%) [10].

QOL and ACHD

EQ-5D dimensions were found to be differently associated with CHD subgroups. Significant differences between the underlying diagnosis were found on all dimensions (p<.001). Compared to all other subgroups, pre-tricuspid shunts were particularly impaired in mobility, daily activities, pain/discomfort and anxiety/depression (***Table 2***). In contrast, complex CHD showed the least problems on the respective descriptive dimensions (***Figure 1-5***).

Similar results were reflected by EQ-5D VAS and index values (p<.001) with EQ-5D VAS values being highest in patients with right heart/pulmonary artery anomalies and complex CHD and lowest in patients with pre-tricuspid shunts. Observed differences were less extreme between descriptive EQ-5D index values. Both EQ-5D values were positively correlated (r=.623, p<.001), with coefficients being the lowest for patients with complex CHD (r=.579, p<.001) and highest for patients with left heart/aortic anomalies (r=.653, p<.001). Variations in QOL were observed depending on the type of measurement

which was applied. Accordingly, the mean VAS score displayed a significantly lower QOL than the descriptive EQ-5D index value.

Socioeconomic Determinants of QOL

OLS-Regression models were applied to analyse relationships of sociodemographic variables with EQ-5D VAS and index values (***Table 3)***. At the 5% level of significance, age had the highest negative impact on VAS values (β=-.32) and Index values (β=-.22). Thus, QOL decreased with advancing age. Patients aged 65+ years indicated the lowest values on both scales. Means for both EQ-values were slightly higher in male than in female patients. Medication intake had significant negative effects on QOL in both measures. Model fit was slightly higher for the dependent variable in VAS values (R^2=.190) than EQ-5D index values (R^2=.112).

Clinical Determinants of QOL

EQ-5D-dimensions were analysed more specifically in regard to different medical features such as connective tissue disease diseases with cardiovascular involvement, cyanotic status and severity codes of CHD. Several ordered logistic regression models were applied using each of the five dimensions as dependent variables (***Table 4***). Generally, patients with comorbidities had significantly increased odds of reporting problems on all dimensions than patients without comorbidities (p<.05). Non-cardiac comorbidities accounted for significantly higher odds of having problems than cardiac comorbidities. No significant effects could be observed for cyanotic status. Furthermore, regression models showed no effects for patients with simple or moderate disease severity classes. It is remarkable that severely classified patients indicated decreased odds of suffering from issues related to mobility or self-care than patients in lower Warnes' classes.

Discussion

QOL is one of the most important measures used to assess the psychosocial impact of chronic disease on a patient's life. This is the first study to investigate patient reported QOL within a cohort of 4,015 patients encompassing a broad spectrum of CHD. QOL in ACHD was assessed by utilizing the EQ-5D-5L, a highly reliable and valid outcome measure within the cardiovascular area [11]. It compromises two types of measurement and therefore provides a global view on QOL in terms of general life satisfaction. This allowed to reveal genuine differences in QOL among patients with different medical and sociodemographic backgrounds, regardless of methodological considerations. Within the context of this study, QOL quantifies the influence of CHD on a patient's ability to function and derive personal satisfaction from life.

QOL in ACHD

In line with previous findings [12], ACHD in general reported a good level of wellbeing which is comparable to German population norms [13]. The two-fold measure of QOL revealed that the type of measurement affects QOL scores differently. Apparently, the overall VAS score indicated a significantly lower QOL than the descriptive EQ-5D index value. One explanation for this discrepancy are differences in the QOL coverage of both measures. It can be assumed that the descriptive system encourages a patient to examine QOL from various angles as the system breaks down QOL into various components. Thus, QOL is regarded as a subjective concept being influenced by multiple causal factors [14]. In contrast, VAS picks up a one-dimensional view of perceived health where patients may indicate a higher occurrence of problems by focusing on somatic health restrictions imposed by their CHD. When comparing the quantitative association of CHD with QOL to other chronic disorders, the average reduction in VAS values in the current sample roughly resembles observations of various other heart diseases [13]. In line with previous research, patients most frequently reported problems in the areas of pain/discomfort (16.3%) and anxiety/depression (14.3%) [15]. These rates lie considerably above German population standards, which document symptoms of anxiety/depression in 4.7% of the general public. This result further supports previous research showing that ACHD are specifically prone to increased psychological distress and therefore require additional psychosocial support [16].

A closer look at different diagnosis groups reveals, that patients with pre-tricuspid shunts were particularly impaired in QOL. Comparable data have previously documented that QOL is not necessarily congruent with the complexity or severity of a heart disease. Even mild primary pre-tricuspid shunts can have a considerable negative impact on QOL [17]. Clinical reality shows that pre-tricuspid shunts are often detected incidentally and later in life creating a different psychological situation than diagnosis of CHD early in life. Children, who grew up with the awareness of their CHD, may acquire a greater sense of appreciation for life and expectations consistent with their capabilities and limitations [18]. From a life-stage perspective, adult developmental tasks may be disrupted by a sudden diagnosis of CHD and patients may experience the effects of their CHD more negatively leading to higher emotional distress. Life-stage variables, such as age at diagnosis or years of survival, need to be further investigated as possible determinants of QOL.

Socioeconomic determinants of QOL

Despite good overall QOL, EQ-5D index and VAS values deteriorated with increasing age. This might be explained by the uncertainty in disease prognosis manifesting itself in an increased sense of vulnerability in this patient group [19]. Most patients with CHD are known to do well in the first decades of life until they eventually develop unexpected age and disease-related comorbidities. This development deserves special attention as the group of ACHD is expected to grow steadily in the future [1].

In contrast to previous findings [12], the present study revealed modest gender-related differences in QOL. Females were more likely to report poor QOL than males. These findings may be attributed to psychosocial factors rather than gender per se [20]. In general, gender is found to influence health expectations, health behaviours and perceived health outcomes [21]. Females may face a triple burden shouldering family responsibility, professional ambition and demands of their chronic disease. Research has demonstrated that females were less likely to return to work, more likely to recline psychological counselling and more socially isolated than males [22]. It has also been argued that females were more willing to disclose problems than males concerning their QOL, which may partly explain the difference in their QOL [21]. Engelfriet et al. (2005) also showed that females with CHD were more often symptomatic and presented functional impairments, despite a higher overall mortality in males over a 5-year period [23]. Gender disparities in patient-provider communication and dissatisfaction with health care might be another reason for decreased QOL in females. They might have higher expectations and a stronger demand for more participatory encounters with their healthcare providers [20]. Improved recognition and understanding of these gender-specific differences and challenges among ACHD is vital to improve their cardiovascular health over the long-term.

Reported medication intake was inversely associated with QOL in the present study This appears plausible because extensive or inappropriate medication can lead to severe side effects and even higher morbidity which may considerably impair QOL [24]. Aside from incorrect pharmaceutical treatment, the daily intake of medication is a constant reminder of illness and may have a negative impact on life satisfaction. Consequently, medication may either be a facilitator by providing new opportunities or an intensifier of problems by adverse psychological and somatic side effects.

Clinical determinants of QOL

Despite all advances in cardiac care, many CHD patients are left with significant residua, sequels or complications from the underlying anomaly [7, 25]. The impact of comorbidities in ACHD is largely underestimated [26]. The current study indicates that the presence of comorbidities increases the risk of problems on all dimensions of the EQ-5D. It is conceivable that affected patients report a lower health status since they may experience serious restrictions in various life domains. As comorbidities become increasingly dominant with advancing age, they may also explain the recorded deterioration of QOL with age in the present sample.

It is remarkable that patients with a more complex CHD scored significantly better in QOL domains. Until now, research has failed to demonstrate a clear-cut correlation between disease complexity and QOL [4]. Although the present finding may seem counterintuitive at first, there are various possible explanations for a better QOL in the light of a chronic condition. Keyes' two continua model of mental health [27] provides an important framework for explaining why patients might experience a good QOL despite their CHD. Accordingly, mental health is a complex state resulting from an interplay of environmental and psychological factors that have a profound influence on one's subjective wellbeing.

Keyes' model holds that mental health (sometimes referred to as mental wellbeing) and mental illness are orthogonally related phenomena and not two endpoints of one single continuum. Although the current state of research confirms elevated levels of mental illness among ACHD [16], this does not necessarily imply impaired mental wellbeing or decreased QOL among these patients. Furthermore, the disability paradox explains why individuals may perceive a high QOL despite serious limitations. Accordingly, QOL depends upon finding a balance in life and maintaining harmonious social relationships [28]. The characteristics associated with a severe CHD may potentially include favourable and compromising factors and thus explain both extremes of QOL in ACHD. Lastly, growing up with a CHD can lead to a so-called "response shift" in terms of redefining priorities in one's life [29]. It is perceivable that patients develop different values from those of healthy persons in the face of a life-threatening, chronic illness. In this context, Sprangers et. al (1999) proposed a theoretical model to clarify and predict changes in QOL as a result of various dispositional characteristics, a patient's health status and mechanisms to accommodate to these changes [30].

Despite the extensive power of the present study, current results should be interpreted with caution due to certain limitations. The study was retrospective and cross-sectional in nature and does not allow to disentangle any conclusions about the directionality of effects or the development of QOL over time. Since all information was based on patient-reported outcomes, medical data may have been classified incorrectly due to a patient's limited knowledge of his or her condition. Consequently, surgical status of patients could not be identified. Subsequently, it would be advisable to synchronize these data with medical records in order to disentangle the effects of empirical-medical observations on QOL. As the enrolment was voluntary, selection bias could not be excluded and may hamper representativeness. Further, this study was performed at a tertiary care center for ACHD which does not reflect the typical population of CHD. The presented data derive solely from patients living in Germany. Generalization of the conclusions and transmission to patients living in other countries or different ethnical groups is debatable. Nonetheless, the obtained results reflect a wide variety of CHD and could therefore be a foundation for diagnosis-specific interventions. Finally, no control group was involved, and data could only be compared to published national EQ-5D studies.

Conclusion

The present study shows that ACHD experience – on aggregate – a good QOL which is indistinguishable from healthy individuals. Against expectation, patients with complex CHD scored higher on QOL. However, specific subgroups of patients indicate significant reductions in QOL and may require extra support in their care to cope with challenges associated with their underlying CHD. The negative correlation with age deserves particular attention as it could lead to a decrease in QOL with the growing median age of this patient population.

QOL is regarded as a central target in the treatment of chronically ill patients. This study supports the need to further assess and promote mental wellbeing in ACHD to safeguard surgical successes of the past decades which have ensured the survival of CHD patients into adulthood. Successful treatment implies not only an increased length of survival but also enhanced subjective wellbeing and QOL.

Declarations

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***Competing Interest*:** The authors have no conflicts of interest to declare.

***Ethics Approval*:** The study was part of the nationwide VEMAH project which was approved on 04/05/2016 by the ethical committee of the Technical University of Munich (157/16S).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: All authors consent to the publication of the manuscript in the Journal "Clinical Researcb in Cardiology".

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions:

(1) Conception and design: CA, SF, HK, LP, RN, JB

(2) Administrative support: All authors

(3) Collection and assembly of data: *CA, SF, SA, UG, LP,MW, RN*

(4) Data analysis and interpretation: CA; SF, LP, JB

(5) Manuscript writing: CA, RN, JB

(6) Final approval of manuscript: All authors.

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Tables

Table 1. Characteristics of the underlying study population.

Variables	n (%)
Age group (n=3,903)	
18-34	1,663 (42.6)
35-64	1,733 (44.4)
65+	507 (13.0)
Gender (n=3,898)	
male	2,087 (53.5)
female	1,811 (46.5)
Residence (n=3,855)	
City	775 (20.1)
Town	590 (15.3)
Rural	2,490 (64.6)
Insurance (n=3,905)	
Public	3,679 (94.2)
Private	219 (5.6)
No Insurance	7 (.2)
Type of CHD (n=4,015)	
Complex Congenital Heart Defects	581 (14.5)
Primary Pre-Tricuspid Shunts	621 (15.5)
Primary post-Tricuspid Shunts	406 (10.1)
Right Heart / Pulmonary artery anomalies	526 (13.1)
Left Heart / Aortic anomalies	898 (22.4)
Miscellaneous CHD	602 (15.0)
Unclassifiable	380 (9.5)
Warnes Class (n=2,778)	
Simple	1,722 (62.0)
Moderate	650 (23.4)
Severe	406 (14.6)

Table 2. Leading diagnosis of CHD and EQ-5D-results.

EQ-5D	Total	Complex Congenital Heart Defects	Primary pre-tricuspid shunts	Primary post-tricuspid shunts	Right Heart / pulmonary artery anomalies	Left Heart / aortic anomalies	Unclassifiable	Miscellaneous	p-Value
Dimension	**n=4,014**	**n=581**	**n=621**	**n=406**	**n=526**	**n=898**	**n=380**	**n=602**	
Mobility	12.2	8.6	13.6	10.4	9.6	10.5	15.0	16.6	<.001*
Self-Care	3.5	2.0	3.0	2.3	3.2	3.5	4.4	4.4	.017*
Usual activities	13.2	13.7	13.5	11.2	12.6	11.1	14.1	16.8	<.001*
Pain/Discomfort	16.3	13.7	20.4	12.3	11.8	14.3	19.5	22.7	<.001*
Anxiety/Depression	14.3	14.8	17.5	14.2	12.6	12.0	14.4	15.5	.002*
EQ-5D VAS	**n=3,761**	**n=540**	**n=605**	**n=388**	**n=485**	**n=844**	**n=351**	**n=548**	<.001*
Mean	76.15	78.21	73.29	77.28	79.50	77.36	74.32	72.80	
SD	18.97	17.12	19.93	19.90	17.48	18.55	19.56	19.57	
EQ-5D Index	**n=3,690**	**n=540**	**n=583**	**n=383**	**n=489**	**n=828**	**n=344**	**n=523**	<.001*
Mean	.90	.92	.89	.91	.92	.91	.88	.87	
SD	.15	.14	.15	.14	.15	.14	.16	.18	

Notes: Data for EQ-5D-dimensions represent relative percentages of patients, who indicated moderate to severe problems with respect to each dimension. Significant differences were calculated using Kruskal-Wallis-tests for independent samples.

Table 3. Patient characteristics and their correspondence with EQ-5D VAS and index values.

	EQ-5D VAS				EQ-5D Index			
Variables	Mean	SD	ß	p	Mean	SD	ß	p
Age group			-.32	<.001*			-.22	<.001*
18-34	83.46	14.75			.94	.11		
35-64	73.44	18.99			.89	.15		
65+	62.23	20.83			.82	.21		
Sex			.01	<.001*			.04	.004
Female	76.11	19.07			.90	.15		
Male	76.55	18.85			.91	.14		
Residence			.02	.084			.03	.060
City	76.30	17.49			.90	.15		
Town	77.08	18.26			.90	.15		
Rural	76.01	19.46			.90	.15		
Medication			-.22	<.001*			-.19	<.001*
No	79.16	17.13			.92	.13		
Yes	65.17	20.69			.83	.20		

Notes: Multivariate analysis was performed using OLS-regression models with EQ-5D VAS and Index values as dependent variables.

Table 4. Impact of medical features with respect to EQ-5D-dimensions.

Variable	n	Mobility n=3,070	Self-Care n=3,073	Usual activities n=3,068	Pain/discomfort n=3,051	Anxiety/depression n=3,061
Comorbidities						
Cardiac Comorbidities	1,463	.302* (.25-.36)	.525* (.38-.73)	.348* (.29-.41)	.331* (.28 - .39)	.467* (.40-.54)
Non-Cardiac Comorbidities	819	.263* (.22-.32)	.281* (.20-.39)	.222* (.18-.27)	.311* (.26 - .37)	.243* (.20-.29)
Cyanosis						
Cyanotic	744	.904 (.49-1.68)	.396 (.12-1.26)	.880 (.50-1.56)	1.088 (.65 -1.82)	.850 (.51-1.41)
Acyanotic	2,176	1.452 (.70-3.02)	.774 (.20-3.04)	1.207 (.63-2.30)	1.011 (.58 -1.77)	.695 (.40-1.19)
Warnes class						
Simple	1,722	1.396 (.69 – 2.84)	.707 (.18 – 2.84)	1.109 (.60 – 2.06)	.984 (.57 – 1.69)	.739 (.44 – 1.24)
Moderate	650	.848 (.50 – 1.45)	.538 (.17 – 1.69)	.985 (.60 – 1.61)	.884 (.57 – 1.37)	.921 (.60 – 1.41)
Severe	406	.384* (.19 – .76)	.148* (.04 – .58)	.710 (.39 – 1.30)	.620 (.36 – 1.08)	.742 (.43 – 1.27)

Notes: Displayed are odds ratios, upper and lower bounds (95% CI) respectively which were obtained from several ordered logistic regressions using EQ-dimensions as dependent variable.
** $p < .05$*

Figures

Figure 1: Distribution of scores for Mobility

Figure 2: Distribution of scores for Self-Care

Figure 3: Distribution of scores for Usual Activities

Figure 4: Distribution of scores for Pain/Discomfort

Figure 5: Distribution of scores for Anxiety/Depression

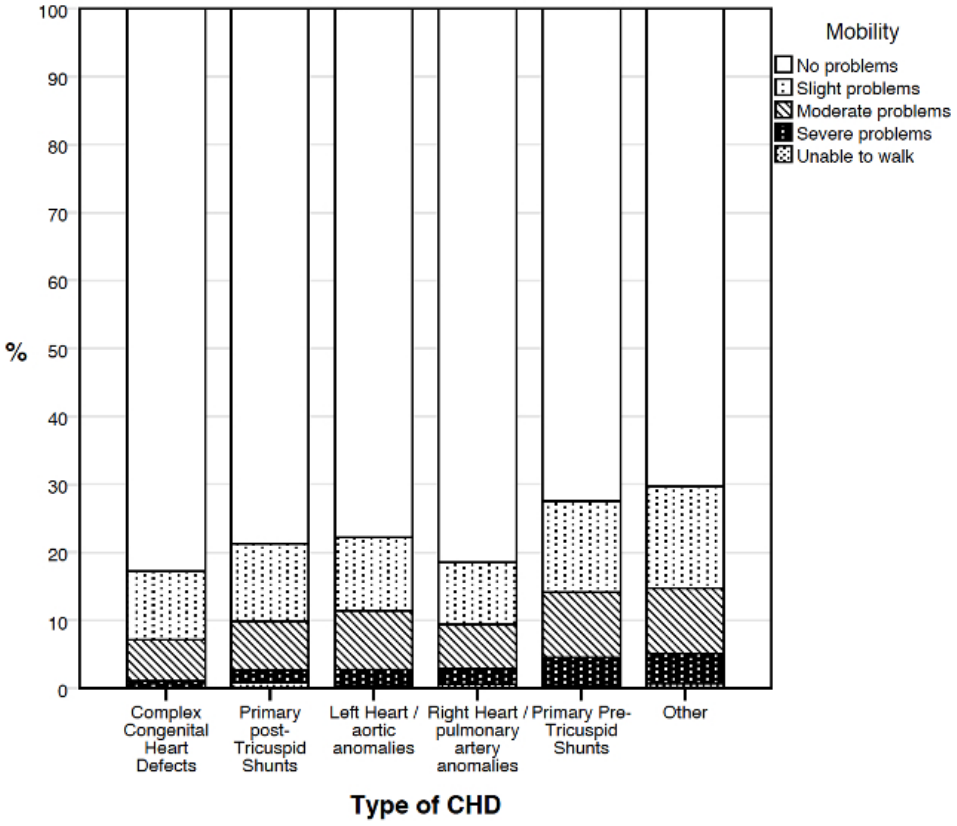

Figure 1: Distribution of scores for Mobility

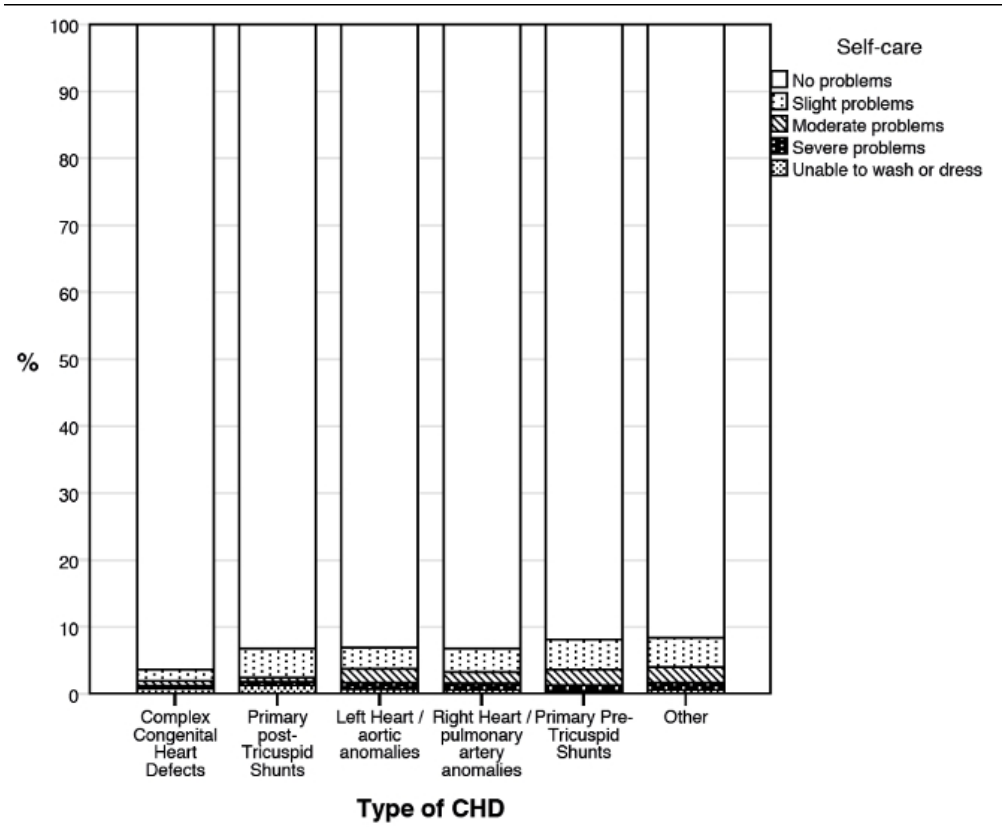

Figure 2: Distribution of scores for Self-Care

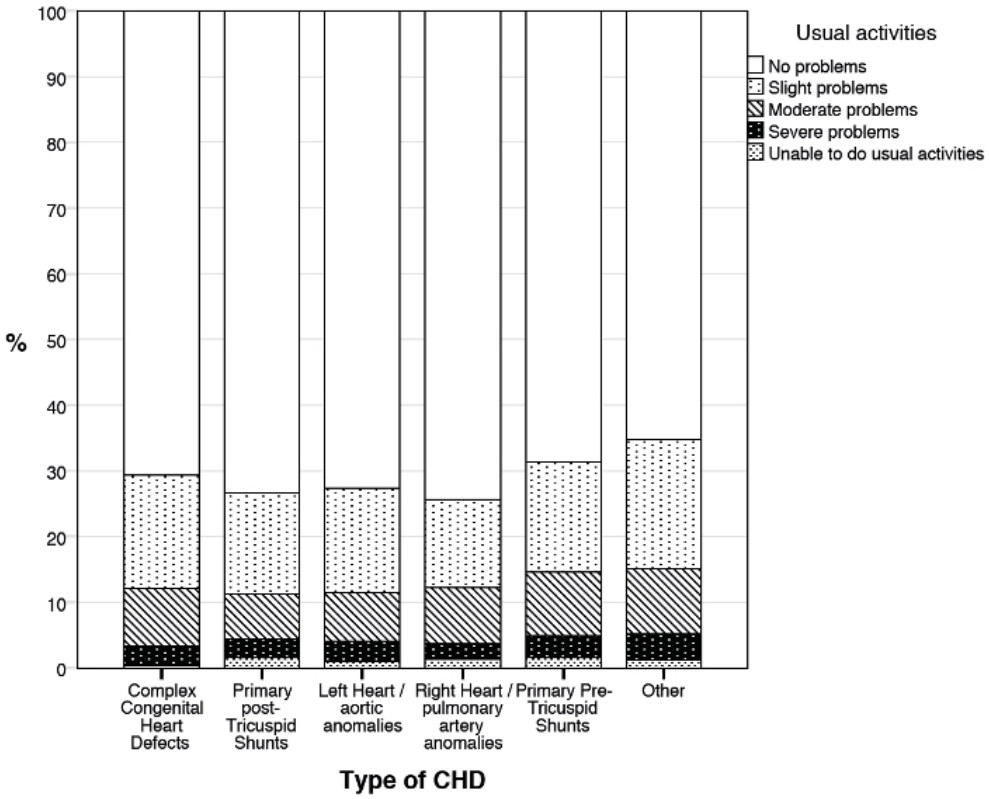

Figure 3: Distribution of scores for Usual Activities

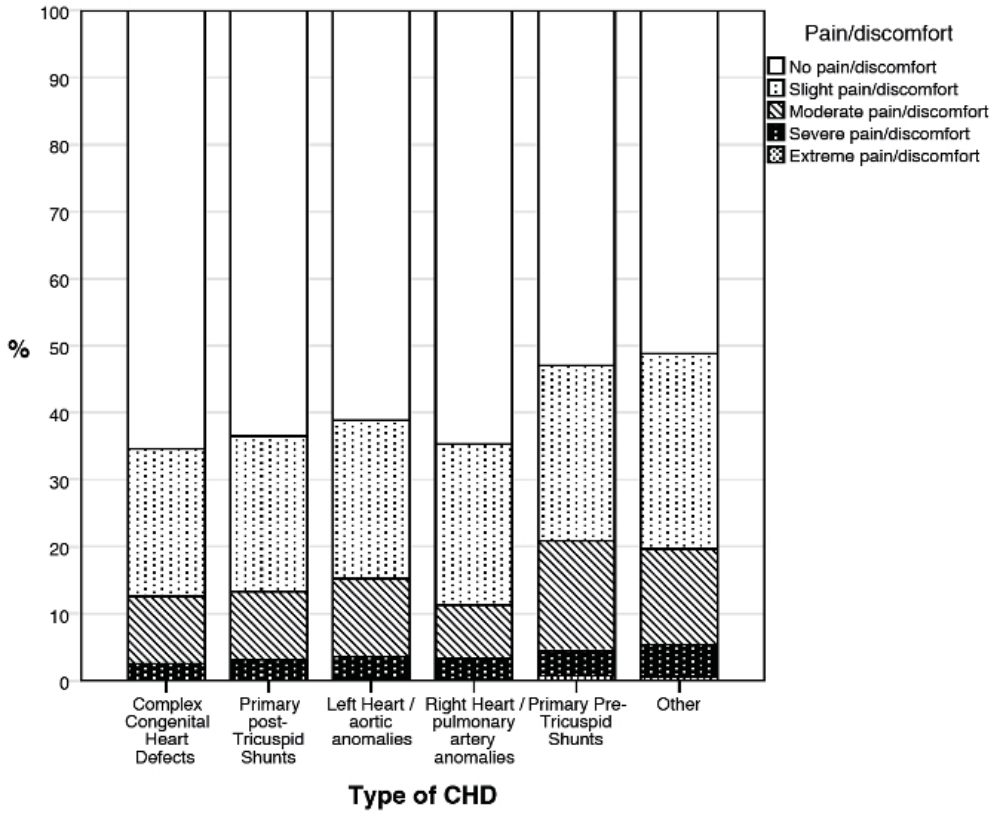

Figure 4: Distribution of scores for Pain/Discomfort

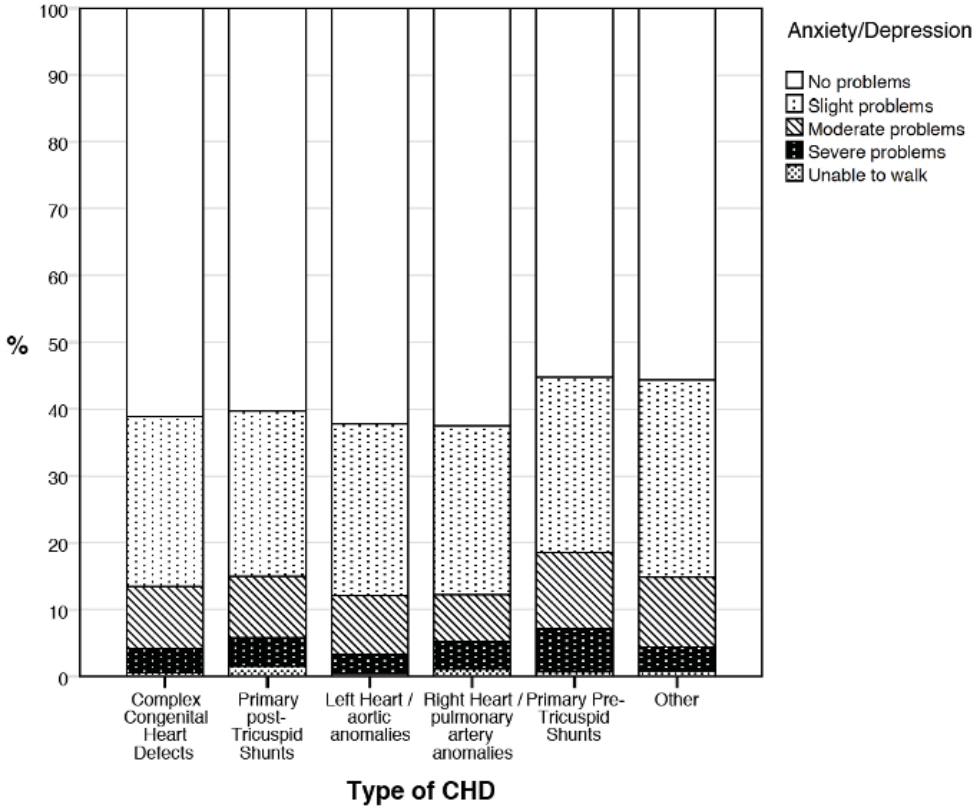

Figure 5: Distribution of scores for Anxiety/Depression

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4/5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4/5
		(*b*) Describe any methods used to examine subgroups and interactions	4/5
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	n/a

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The "Well-being paradox" revisited: A cross-sectional study of quality of life in over 4,000 adults with congenital heart disease

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The "Well-being paradox" revisited: A cross-sectional study of quality of life in over 4,000 adults with congenital heart disease

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Abstract

Objective: The present cross-sectional study investigated quality of life (QOL) in a large cohort of German adults with congenital heart disease (ACHD) in association with patient-related and clinical variables.

Design: Cross-sectional survey.

Participants: Between 2016 and 2019, a representative sample of 4,014 adults with various forms of CHD was retrospectively analyzed. Inclusion criteria were confirmed diagnosis of CHD, participant age 18 years and older, necessary physical, cognitive and language capabilities to complete self-report questionnaires.

Primary and secondary outcome measures: QOL was assessed using the EQ-5D-5L. Sociodemographic and medical information was obtained by a self-devised questionnaire. Associations of QOL with patient-reported clinical and sociodemographic variables were quantified using multiple regression analysis and multiple ordinal logit models.

Results: Overall, ACHD (41.8 ± 17.2 years; 46.5% female) reported a good QOL comparable to German population norms. The most frequently reported complaints occurred in the dimensions pain/discomfort (mean: 16.3, SD: $p<0.001$) and anxiety/depression (mean: 14.3, $p<0.001$). QOL differed significantly within ACHD subgroups, with patients affected by pre-tricuspid shunt lesions indicating the most significant impairments ($p<0.001$). Older age, female sex, medication intake and the presence of comorbidities, were associated with significant reductions in QOL ($p<0.001$). CHD severity was positively associated with QOL within the dimensions of self-care (odds ratio [OR] 0.148, 95% CI .04-.58) and mobility (odds ratio [OR] 0.384, 95% CI .19-.76).

Conclusion: Current findings temper widely held assumptions among clinicians and confirm that ACHD experience a generally good QOL. However, specific subgroups may require additional support to cope with disease-related challenges. The negative correlation of QOL with age is especially alarming as the population of ACHD is expected to grow older in the future.

Keywords: *adults with congenital heart disease; psychological situation; quality of life; prevention; EQ5D*

Strenghts and Limitations

- First study of its kind exploring quality of life (QOL) among 4,014 patients with different medical and patient-related backgrounds.
- Uniform conceptualization of QOL based on EQ-5D-5L, which is a highly reliable and valid outcome measure within the cardiovascular area.
- Present findings help clinicians to identify specific subsets of patients who require extra psychological support and therefore constitute a major step in paving the way towards integrative cardiac care.
- Causal inferences are not possible due to the cross-sectional design of this study.
- Ambiguous findings open new avenues for future research in understanding the construction of self-rated health despite or as a consequence of CHD.

Introduction

Congenital heart defects (CHD) are the most common isolated inborn organ malformations and affect 1.35–1.5 million children each year. Although 90% of patients with CHD survive into adulthood, many of them are not cured and need to adapt to their chronic medical condition throughout their lives [1]. Besides symptoms related to their heart disease, lifelong psychosocial impairments may seriously impact the patients´ perceived quality of life (QOL) [2]. While clinical research traditionally focused on objective medical outcomes, the relevance of QOL and various related patient-reported outcomes is increasingly recognized in the evaluation of care for adults with congenital heart disease (ACHD) [3].

Research on QOL in ACHD is still relatively scarce and not conclusive. Empirical findings indicate that QOL among ACHD is compromised by sociodemographic factors (unemployment, older age, single status), psychological features (negative illness perceptions, distressed personality) and medical characteristics (e.g. hospitalization, worse functional status). QOL has been found to be positively associated with higher socioeconomic and educational status, stronger social support, better functional class, better knowledge of CHD, stronger sense of coherence as well as the absence of cardiac surgery. Existing findings are inconsistent regarding cardiovascular status, medication, age, and gender, although these variables appeared to be the most frequently investigated determinants [4].

These inconsistent results of existing research on QOL in ACHD can be attributed to a lack of a clear conceptual background, inconsistent methods and insufficient sample sizes [4]. Additionally, the high heterogeneity of ACHD constitutes a substantial confounding factor due to their great anatomical and clinical disease complexity. Most studies on QOL in ACHD focused on specific subgroups of patients which limits their informational value. Consequently, clinical parameters were not sufficiently examined to explain potential differences in QOL by the underlying diagnosis or severity of CHD. Although a recent review attests temporal qualitative improvements in QOL studies over the last decades, the current research situation still fails to meet scientific quality criteria [5].

The present study aimed to assess QOL within a large sample of ACHD in Germany and examine potential determinants of QOL in terms of patient-related and medical characteristics. Identifying determinants of QOL along with special needs of ACHD could advance the improvement of health care for this growing patient population.

Methods

Design

The present study represents a sub-analysis of the nationwide VEMAH initiative (“Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern”, engl. “Medical Care Situation of ACHD”). Detailed information on the rationale, design, and methods is documented in a former published paper

[6]. VEMAH is a multicenter, cross-sectional study to assess the health care situation of ACHD in Germany. Coordination of VEMAH was initiated and carried out by the German Heart Center Munich.

Population

A questionnaire package was consecutively addressed to ACHD presenting at the Department of Congenital Heart Disease and Pediatric Cardiology of the German Heart Center Munich and the Department of Cardiology of the University of Erlangen. Additionally, the health insurance provider "AOK Bayern" distributed questionnaires to their policyholders with CHD in Bavaria, and the "National Register for Congenital Heart Defects" in Berlin, Germany, invited its members to participate in the study online. Guidelines on good clinical practice and data protection guidelines were followed. Inclusion criteria were: (1) confirmed diagnosis of CHD according to the definition of Thiene & Frescura, [7] (2) participant age 18 years and older, (3) necessary physical, cognitive and language capabilities to complete self-report questionnaires.

Measures

Patients completed a questionnaire either in person, online or by mail. Data collection took place between 2016 and 2019. QOL was measured using the generic questionnaire EQ-5D-5L[8].

I. *Demographic and clinical information*

Sociodemographic and medical information was obtained by a self-devised questionnaire. Medical variables included leading CHD, medication, presence of cyanosis, (non-) cardiac comorbidities and hereditary diseases. Following the recommendations of the American College of Cardiology, patients were divided into three severity groups based on their CHD diagnosis (ACC) [9].

II. *Quality of Life (EQ-5D-5L)*

QOL was measured using the updated five-level version of the EQ-5D [8] which provides a simple, generic measure of a patient's perceived health status. The EQ-5D-5L consists of a descriptive system questionnaire and a visual analogue scale (VAS). The descriptive system compromises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each patient was asked to indicate his perceived impairments on a 5-point Likert scale ranging from "no problems" to "extreme problems/unable". Responses were converted into a single weighted index score (EQ-5D index) which indicates how good or poorthe respondent´s health status is based on existing population norms. A value set for the EQ-5D-5L, based on a representative sample of the German population, has recently been developed [10]. The VAS indicates a patient's overall health state on the day of the questionnaire completion. It is a scale which ranges from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine") and provides a quantitative measure of a patient's perceived health. The EQ-

5D-5L proved to be a reliable and valid method for measuring QOL in cardiovascular populations (Cronbach's alpha = 0.856) [11].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 (IBM, Armond, New York, United States). Descriptive measures were calculated for sample characteristics, including patient reported sociodemographic and medical variables (absolute and relative frequencies, mean and standard deviations). The relationships between CHD diagnosis groups and EQ-5D-index values, including the underlying dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression were analysed. The comparison of ordinally scaled values was based on cumulative frequencies representing the relative proportion of patients with moderate to severe symptoms on the specific dimensions. Kruskal-Wallis-tests were applied to reveal significant differences between EQ-5D-dimensions and metric index values. Furthermore, the relationship between both EQ-5D VAS scores and dedicated index values was analysed with respect to various patient characteristics. Multiple regression models using Ordinary least squares (OLS)-estimates were calculated, while bivariate Pearson-coefficients were used to analyse the correlation between VAS and index scores. Finally, multiple ordinal logit models were applied to identify significant predictors of the respective QOL dimensions. For all tests, the statistical significance level was set at $p < 0.05$.

Patient and Public Involvement

Neither patients nor the public were involved in the design and conduct of this research. The methodology of this research was adapted in multidisciplinary collaboration.

Results

Sample characteristics

A total of 4,014 patients was analysed (46.5% female) (***Table 1).*** The mean age of ACHD was 41.8 ± 17.2 [18-97] years. Patients were subclassified according to the underlying CHD into six main groups, consisting of complex CHD (n=581); pre-tricuspid shunts (n=621); post-tricuspid shunts (n=406); right heart or pulmonary artery anomalies (n=526); left heart or aortic anomalies (n=898); and miscellaneous CHD (n=602). 15.4 % of patients (n=602) presented with cyanosis. The severity of CHD was determined according to the Warnes classification system as simple (n=1,722, 62.0%), intermediate (n=650, 23.4%) or severe (n=406, 14.6%) [12].

QOL and ACHD

EQ-5D dimensions were found to be differently associated with CHD subgroups. Significant differences between the underlying diagnosis were found on all dimensions (p<.001). Compared to all other subgroups, pre-tricuspid shunts were particularly impaired in mobility, daily activities, pain/discomfort and anxiety/depression (***Table 2***). In contrast, complex CHD showed the least problems on the respective descriptive dimensions (***Figure 1-5***).

Similar results were reflected by EQ-5D VAS and index values (p<.001) with EQ-5D VAS values being highest in patients with right heart/pulmonary artery anomalies and complex CHD and lowest in patients with pre-tricuspid shunts. Observed differences were less extreme between descriptive EQ-5D index values. Both EQ-5D values were positively correlated (r=.623, p<.001), with coefficients being the lowest for patients with complex CHD (r=.579, p<.001) and highest for patients with left heart/aortic anomalies (r=.653, p<.001). Variations in QOL were observed depending on the type of measurement which was applied. Accordingly, the mean VAS score displayed a significantly lower QOL than the descriptive EQ-5D index value.

Patient-related Determinants of QOL

OLS-Regression models were applied to analyse relationships of sociodemographic variables with EQ-5D VAS and index values (***Table 3)***. At the 5% level of significance, age had the highest negative impact on VAS values (β=-.32) and Index values (β=-.22). Thus, QOL decreased with advancing age. Patients aged 65+ years indicated the lowest values on both scales. Means for both EQ-values were slightly higher in male than in female patients. Medication intake had significant negative effects on QOL in both measures. Model fit was slightly higher for the dependent variable in VAS values (R^2=.190) than EQ-5D index values (R^2=.112).

CHD-related Determinants of QOL

EQ-5D-dimensions were analysed more specifically in regard to different medical features such as connective tissue disease diseases with cardiovascular involvement, cyanotic status and severity codes of CHD. Several ordered logistic regression models were applied using each of the five dimensions as dependent variables (***Table 4***). Generally, patients with comorbidities had significantly increased odds of reporting problems on all dimensions than patients without comorbidities (p<.05). Non-cardiac comorbidities accounted for significantly higher odds of having problems than cardiac comorbidities. No significant effects could be observed for cyanotic status. Furthermore, regression models showed no effects for patients with simple or moderate disease severity classes. Apparently,severely classified patients indicated decreased odds of suffering from issues related to mobility or self-care than patients in lower Warnes' classes.

Discussion

QOL is one of the most important measures used to assess the psychosocial impact of chronic disease on a patient's life. This is the first study to investigate patient reported QOL within a cohort of 4,014 patients encompassing a broad spectrum of CHD. QOL in ACHD was assessed by utilizing the EQ-5D-5L, a highly reliable and valid outcome measure within the cardiovascular area [13]. It compromises two types of measurement and therefore provides a global view on QOL in terms of general life satisfaction. This allowed to reveal genuine differences in QOL among patients with different medical and sociodemographic backgrounds, regardless of methodological considerations. Within the context of this study, QOL quantifies the influence of CHD on a patient's ability to function and derive personal satisfaction from life.

QOL in ACHD

In line with previous findings [14], ACHD in general reported a good level of wellbeing which is comparable to German population norms [15]. The two-fold measure of QOL revealed that the type of measurement affects QOL scores differently. Apparently, the overall VAS score indicated a significantly lower QOL than the descriptive EQ-5D index value. One explanation for this discrepancy are differences in the QOL coverage of both measures. It can be assumed that the descriptive system encourages a patient to examine QOL from various angles as the system breaks down QOL into various components. Thus, QOL is regarded as a subjective concept being influenced by multiple causal factors [16]. In contrast, VAS picks up a one-dimensional view of perceived health where patients may indicate a higher occurrence of problems by focusing on somatic health restrictions imposed by their CHD. When comparing the quantitative association of CHD with QOL to other chronic disorders, the average reduction in VAS values in the current sample roughly resembles observations of various other heart diseases [15]. In line with previous research, patients most frequently reported problems in the areas of pain/discomfort (16.3%) and anxiety/depression (14.3%) [17]. These rates lie considerably above German population standards, which document symptoms of anxiety/depression in 4.7% of the general public. This result further supports previous research showing that ACHD are specifically prone to increased psychological distress and therefore require additional psychosocial support [18].

A closer look at different diagnosis groups reveals, that patients with pre-tricuspid shunts were particularly impaired in QOL. Comparable data have previously documented that QOL is not necessarily congruent with the complexity or severity of a heart disease. Even mild primary pre-tricuspid shunts can have a considerable negative impact on QOL [19]. Clinical reality shows that pre-tricuspid shunts are often detected incidentally and later in life creating a different psychological situation than diagnosis of CHD early in life. Children, who grew up with the awareness of their CHD, may acquire a greater sense of appreciation for life and expectations consistent with their capabilities and limitations [20]. Qualitative research on ACHD indicates that patients perceive the awareness of their childhood condition as a ressource to re-evaluate life priorities and develop a new life perspective [21]. A recent

study has further established, that sense of coherence is a highly significant predictor of QOL in ACHD [22]. Based on theoretical considerations, SOC develops during childhood and is thought to be fully developed by the age of 30 years [23]. Patients who may be diagnosed later in life may have missed the chance to develop and refine coping mechanisms and may thereforeexperience the effects of their CHD more negatively leading to higher emotional distress. Life-stage variables, such as age at diagnosis or years of survival, need to be further investigated as possible determinants of QOL.

Socioeconomic determinants of QOL

Despite good overall QOL, EQ-5D index and VAS values deteriorated with increasing age. This might be explained by the uncertainty in disease prognosis manifesting itself in an increased sense of vulnerability in this patient group [24]. Most patients with CHD are known to do well in the first decades of life until they eventually develop unexpected age and disease-related comorbidities. This development deserves special attention as the group of ACHD is expected to grow steadily in the future [1].

In contrast to previous findings [14], the present study revealed modest gender-related differences in QOL. Females were more likely to report poor QOL than males. These findings may be attributed to psychosocial factors rather than gender per se [25]. In general, gender is found to influence health expectations, health behaviours and perceived health outcomes [26]. Females may face a triple burden shouldering family responsibility, professional ambition and demands of their chronic disease. Research has demonstrated that females were less likely to return to work, more likely to recline psychological counselling and more socially isolated than males [27]. It has also been argued that females were more willing to disclose problems than males concerning their QOL, which may partly explain the difference in their QOL [26]. Engelfriet et al. (2005) also showed that females with CHD were more often symptomatic and presented functional impairments, despite a higher overall mortality in males over a 5-year period [28]. Gender disparities in patient-provider communication and dissatisfaction with health care might be another reason for decreased QOL in females. They might have higher expectations and a stronger demand for more participatory encounters with their healthcare providers [25]. Improved recognition and understanding of these gender-specific differences and challenges among ACHD is vital to improve their cardiovascular health over the long-term.

Reported medication intake was inversely associated with QOL in the present study This appears plausible because extensive or inappropriate medication can lead to severe side effects and even higher morbidity which may considerably impair QOL [29]. Aside from incorrect pharmaceutical treatment, the daily intake of medication is a constant reminder of illness and may have a negative impact on life satisfaction. Consequently, medication may either be a facilitator by providing new opportunities or an intensifier of problems by adverse psychological and somatic side effects.

Clinical determinants of QOL

Despite all advances in cardiac care, many CHD patients are left with significant residua, sequels or complications from the underlying anomaly [9, 30]. The impact of comorbidities in ACHD is largely underestimated [31]. The current study indicates that the presence of comorbidities increases the risk of problems on all dimensions of the EQ-5D. It is conceivable that affected patients report a lower health status since they may experience serious restrictions in various life domains. As comorbidities become increasingly dominant with advancing age, they may also explain the recorded deterioration of QOL with age in the present sample.

It is remarkable that patients with a more complex CHD scored significantly better in QOL domains. Until now, research has failed to demonstrate a clear-cut correlation between disease complexity and QOL [4]. Although the present finding may seem counterintuitive at first, there are various possible explanations for a better QOL in the light of a chronic condition. Keyes' two continua model of mental health [32] provides an important framework for explaining why patients might experience a good QOL despite their CHD. Accordingly, mental health is a complex state resulting from an interplay of environmental and psychological factors that have a profound influence on one's subjective wellbeing. Keyes' model holds that mental health (sometimes referred to as mental wellbeing) and mental illness are orthogonally related phenomena and not two endpoints of one single continuum. Although the current state of research confirms elevated levels of mental illness among ACHD [18], this does not necessarily imply impaired mental wellbeing or decreased QOL among these patients. Furthermore, the disability paradox explains why individuals may perceive a high QOL despite serious limitations. Accordingly, QOL depends upon finding a balance in life and maintaining harmonious social relationships [33]. The characteristics associated with a severe CHD may potentially include favourable and compromising factors and thus explain both extremes of QOL in ACHD. Lastly, growing up with a CHD can lead to a so-called "response shift" in terms of redefining priorities in one's life [34]. It is perceivable that patients develop different values from those of healthy persons in the face of a life-threatening, chronic illness. In this context, Sprangers et. al (1999) proposed a theoretical model to clarify and predict changes in QOL as a result of various dispositional characteristics, a patient's health status and mechanisms to accommodate to these changes [35].

Despite the extensive power of the present study, current results should be interpreted with caution due to certain limitations. The study was retrospective and cross-sectional in nature and does not allow to disentangle any conclusions about the directionality of effects or the development of QOL over time. Since all information was based on patient-reported outcomes, medical data may have been classified incorrectly due to a patient's limited knowledge of his or her condition. Consequently, surgical status of patients could not be identified. Subsequently, it would be advisable to synchronize these data with medical records in order to disentangle the effects of empirical-medical observations on QOL. As the enrolment was voluntary, selection bias could not be excluded and may hamper representativeness. Further, this study was performed at a tertiary care center for ACHD which does not reflect the typical

population of CHD. Further doubts must be raised about whether the applied EQ-5D-5L provides an accurate tool to evaluate QOL among AHCD. Although the updated 5L version demonstrates superior performance compared to its predecessor, psychometric properties in terms of high ceiling effects and weak discriminatory power have previously been questioned [36]. It has further been shown that the choice of value set has an impact on EQ-5D scores [37]. Since the present study used a population-based value set to construct QOL estimates, we strongly encourage to re-evaluate current findings on the basis of experience-based value sets. Further, the inventory was administered in three different ways. However, measurement invariance across the survey methods was not tested and the equivalence across the survey methods remains questionable. Since the primary aim of this study was to assess clinical determinants of QOL, sociodemographic variables were not explicitly reviewed within the present analysis. Based on the German healthcare system, the depicted sociodemographic variables are crucial indicators of access to medical supply and were therefore separately analyzed. Given previously documented associations between sociodemographic factors and QOL, generalization of the conclusions and transmission to patients from differing socioeconomic conditions is debatable. The present survey assessed biological sex with a binary value. Given the increasing incidence of transgender and gender non-binary individuals and that large health disparities exist for this population [38], future research should increasingly expand measures of sex/gender to be trans inclusive. Finally, no control group was involved, and data could only be compared to published national EQ-5D studies.

Conclusion

The present study shows that ACHD experience – on aggregate – a good QOL which is indistinguishable from healthy individuals. Against expectation, patients with complex CHD scored higher on QOL. However, specific subgroups of patients indicate significant reductions in QOL and may require extra support in their care to cope with challenges associated with their underlying CHD. The negative correlation with age deserves particular attention as it could lead to a decrease in QOL with the growing median age of this patient population.

QOL is regarded as a central target in the treatment of chronically ill patients. This study supports the need to further assess and promote mental wellbeing in ACHD to safeguard surgical successes of the past decades which have ensured the survival of CHD patients into adulthood. Successful treatment implies not only an increased length of survival but also enhanced subjective wellbeing and QOL.

Declarations

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***Competing Interest*:** The authors have no conflicts of interest to declare.

***Ethics Approval*:** The study was part of the nationwide VEMAH project which was approved on 04/05/2016 by the ethical committee of the Technical University of Munich (157/16S).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: All authors consent to the publication of the manuscript in the Journal "Clinical Researcb in Cardiology".

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions:

(1) Conception and design: CA, HK, JB

(2) Administrative support: CA, SF, SA, PE, UG, JH, HK, LP, MW, RN, JB

(3) Collection and assembly of data: *CA, SF, SA, UG, MW*

(4) Data analysis and interpretation: CA; SF

(5) Manuscript writing: CA, JB

(6) Final approval of manuscript: CA, SF, SA, PE, UG, JH, HK, LP, MW, RN, JB

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Tables

Table 1. Characteristics of the underlying study population.

Variables	n (%)
Age group (n=3,903)	
18-34	1,663 (42.6)
35-64	1,733 (44.4)
65+	507 (13.0)
Gender (n=3,898)	
male	2,087 (53.5)
female	1,811 (46.5)
Residence (n=3,855)	
City	775 (20.1)
Town	590 (15.3)
Rural	2,490 (64.6)
Insurance (n=3,905)	
Public	3,679 (94.2)
Private	219 (5.6)
No Insurance	7 (.2)
Type of CHD (n=4,014)	
Complex Congenital Heart Defects	581 (14.5)
Primary Pre-Tricuspid Shunts	621 (15.5)
Primary post-Tricuspid Shunts	406 (10.1)
Right Heart / Pulmonary artery anomalies	526 (13.1)
Left Heart / Aortic anomalies	898 (22.4)
Miscellaneous CHD	602 (15.0)
Unclassifiable	380 (9.5)
Warnes Class (n=2,778)	
Simple	1,722 (62.0)
Moderate	650 (23.4)
Severe	406 (14.6)

Table 2. Leading diagnosis of CHD and EQ-5D-results.

EQ-5D	Total	Complex Congenital Heart Defects	Primary pre-tricuspid shunts	Primary post-tricuspid shunts	Right Heart / pulmonary artery anomalies	Left Heart / aortic anomalies	Unclassifiable	Miscellaneous	p-Value
Dimension	**n=4,014**	**n=581**	**n=621**	**n=406**	**n=526**	**n=898**	**n=380**	**n=602**	
Mobility	12.2	8.6	13.6	10.4	9.6	10.5	15.0	16.6	<.001*
Self-Care	3.5	2.0	3.0	2.3	3.2	3.5	4.4	5.4	.017*
Usual activities	13.2	13.7	13.5	11.2	12.6	11.1	14.1	16.8	<.001*
Pain/Discomfort	16.3	13.7	20.4	12.3	11.8	14.3	19.5	22.7	<.001*
Anxiety/Depression	14.3	14.8	17.5	14.2	12.6	12.0	14.4	15.5	.002*
EQ-5D VAS	**n=3,761**	**n=540**	**n=605**	**n=388**	**n=485**	**n=844**	**n=351**	**n=548**	<.001*
Mean	76.15	78.21	73.29	77.28	79.50	77.36	74.32	72.80	
SD	18.97	17.12	19.93	19.90	17.48	18.55	19.56	19.57	
EQ-5D Index	**n=3,690**	**n=540**	**n=583**	**n=383**	**n=489**	**n=828**	**n=344**	**n=523**	<.001*
Mean	.90	.92	.89	.91	.92	.91	.88	.87	
SD	.15	.14	.15	.14	.15	.14	.16	.18	

Notes: Data for EQ-5D-dimensions represent relative percentages of patients, who indicated moderate to severe problems with respect to each dimension. Significant differences were calculated using Kruskal-Wallis-tests for independent samples.

Table 3. Patient characteristics and their correspondence with EQ-5D VAS and index values.

	EQ-5D VAS				EQ-5D Index			
Variables	Mean	SD	ß	p	Mean	SD	ß	p
Age group			-.32	<.001*			-.22	<.001*
18-34	83.46	14.75			.94	.11		
35-64	73.44	18.99			.89	.15		
65+	62.23	20.83			.82	.21		
Sex			.01	<.001*			.04	.004
Female	76.11	19.07			.90	.15		
Male	76.55	18.85			.91	.14		
Residence			.02	.084			.03	.060
City	76.30	17.49			.90	.15		
Town	77.08	18.26			.90	.15		
Rural	76.01	19.46			.90	.15		
Medication			-.22	<.001*			-.19	<.001*
No	79.16	17.13			.92	.13		
Yes	65.17	20.69			.83	.20		

Notes: Multivariate analysis was performed using OLS-regression models with EQ-5D VAS and Index values as dependent variables.

Table 4. Impact of medical features with respect to EQ-5D-dimensions.

Variable	n	**Mobility** n=3,070	**Self-Care** n=3,073	**Usual activities** n=3,068	**Pain/discomfort** n=3,051	**Anxiety/depression** n=3,061
Comorbidities						
Cardiac Comorbidities	1,463	.302* (.25-.36)	.525* (.38-.73)	.348* (.29-.41)	.331* (.28 - .39)	.467* (.40-.54)
Non-Cardiac Comorbidities	819	.263* (.22-.32)	.281* (.20-.39)	.222* (.18-.27)	.311* (.26 - .37)	.243* (.20-.29)
Cyanosis						
Cyanotic	744	.904 (.49-1.68)	.396 (.12-1.26)	.880 (.50-1.56)	1.088 (.65 -1.82)	.850 (.51-1.41)
Acyanotic	2,176	1.452 (.70-3.02)	.774 (.20-3.04)	1.207 (.63-2.30)	1.011 (.58 -1.77)	.695 (.40-1.19)
Warnes class						
Simple	1,722	1.396 (.69 – 2.84)	.707 (.18 – 2.84)	1.109 (.60 – 2.06)	.984 (.57 – 1.69)	.739 (.44 – 1.24)
Moderate	650	.848 (.50 – 1.45)	.538 (.17 – 1.69)	.985 (.60 – 1.61)	.884 (.57 – 1.37)	.921 (.60 – 1.41)
Severe	406	.384* (.19 – .76)	.148* (.04 – .58)	.710 (.39 – 1.30)	.620 (.36 – 1.08)	.742 (.43 – 1.27)

Notes: Displayed are odds ratios, upper and lower bounds (95% CI) respectively which were obtained from several ordered logistic regressions using EQ-dimensions as dependent variable.
** $p < .05$*

Figures

Figure 1: Distribution of scores for Mobility

Figure 2: Distribution of scores for Self-Care

Figure 3: Distribution of scores for Usual Activities

Figure 4: Distribution of scores for Pain/Discomfort

Figure 5: Distribution of scores for Anxiety/Depression

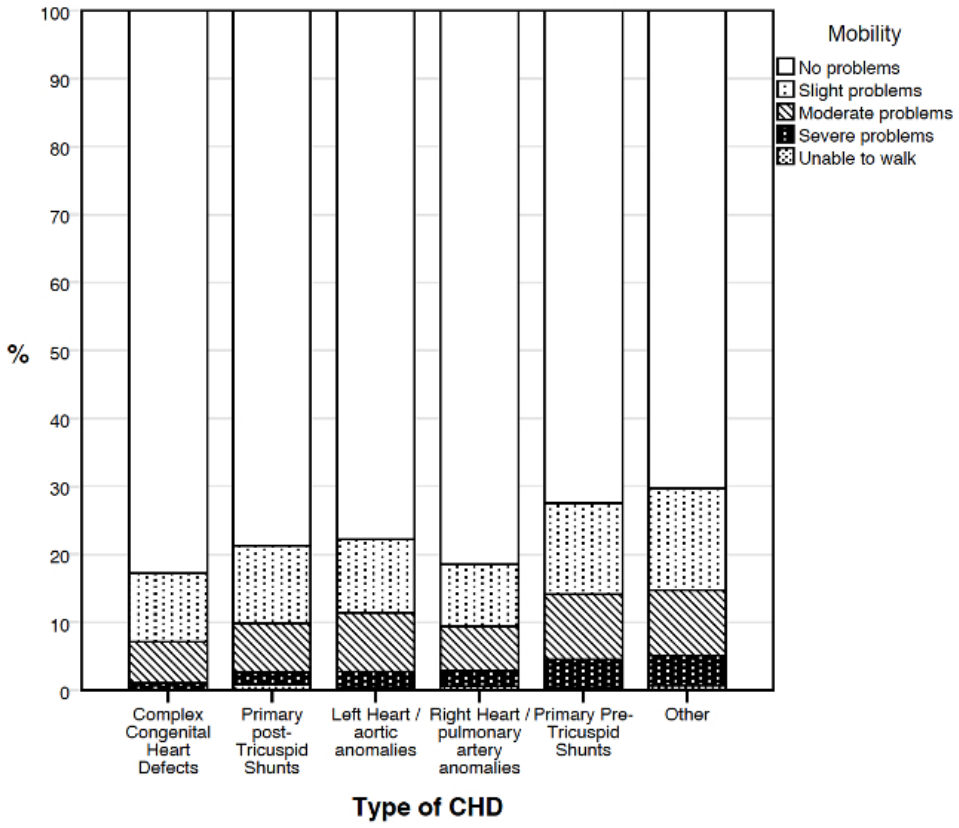

Figure 1: Distribution of scores for Mobility

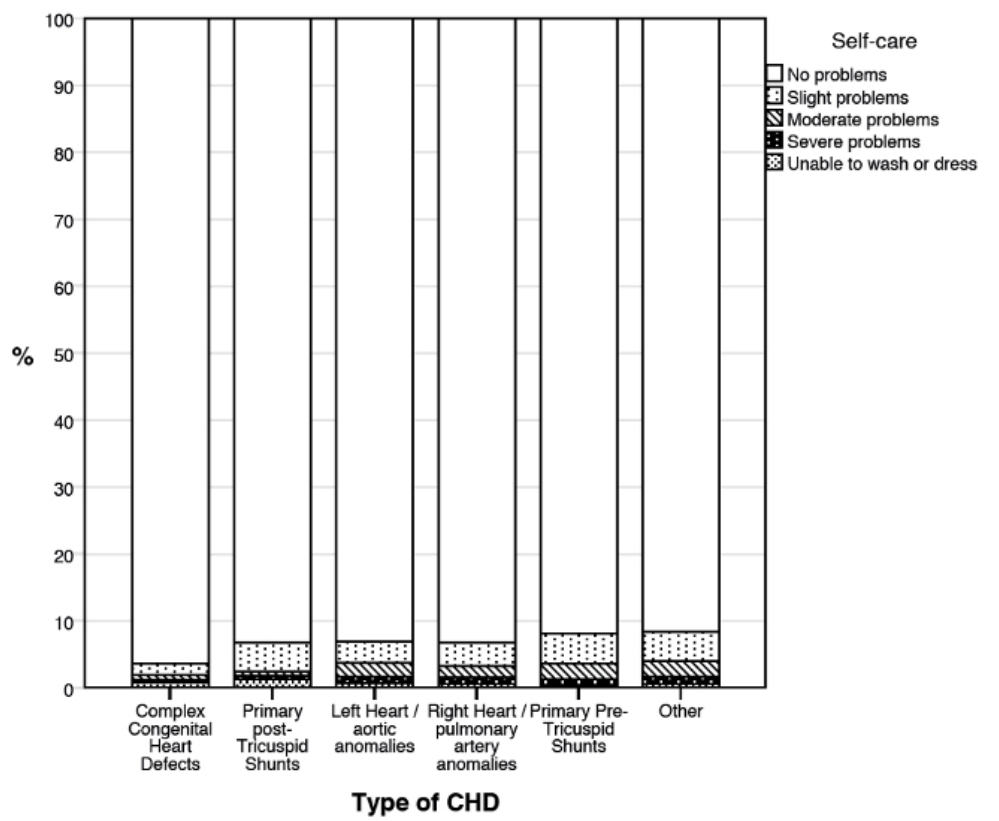

Figure 2: Distribution of scores for Self-Care

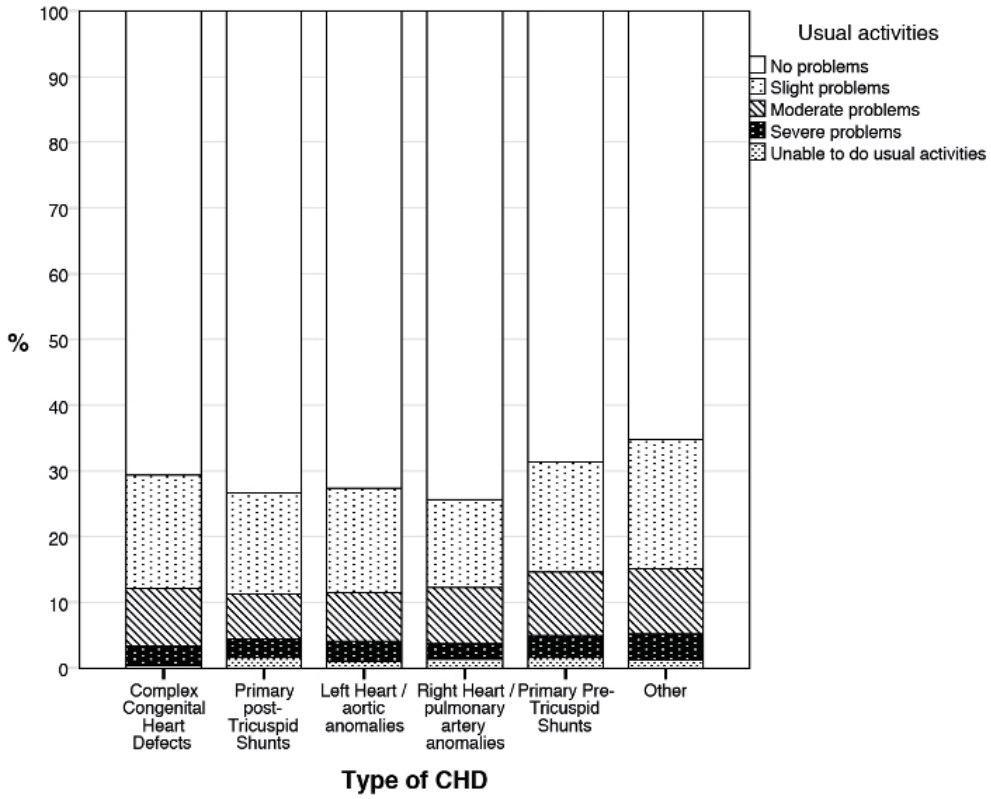

Figure 3: Distribution of scores for Usual Activities

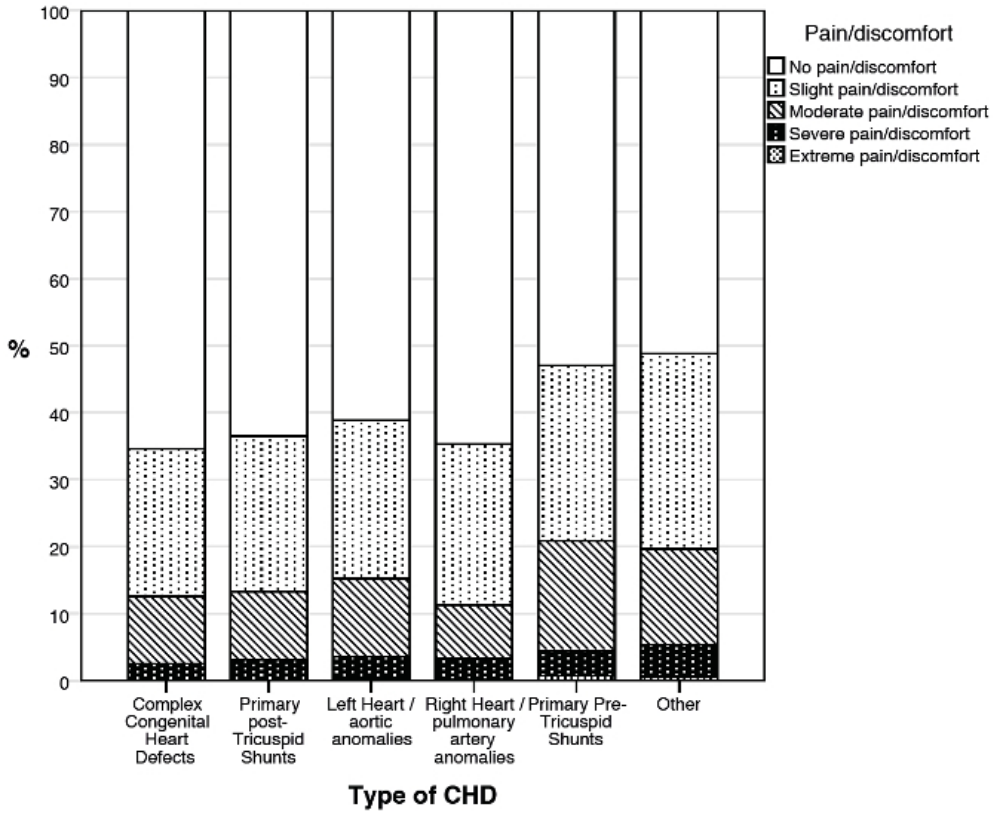

Figure 4: Distribution of scores for Pain/Discomfort

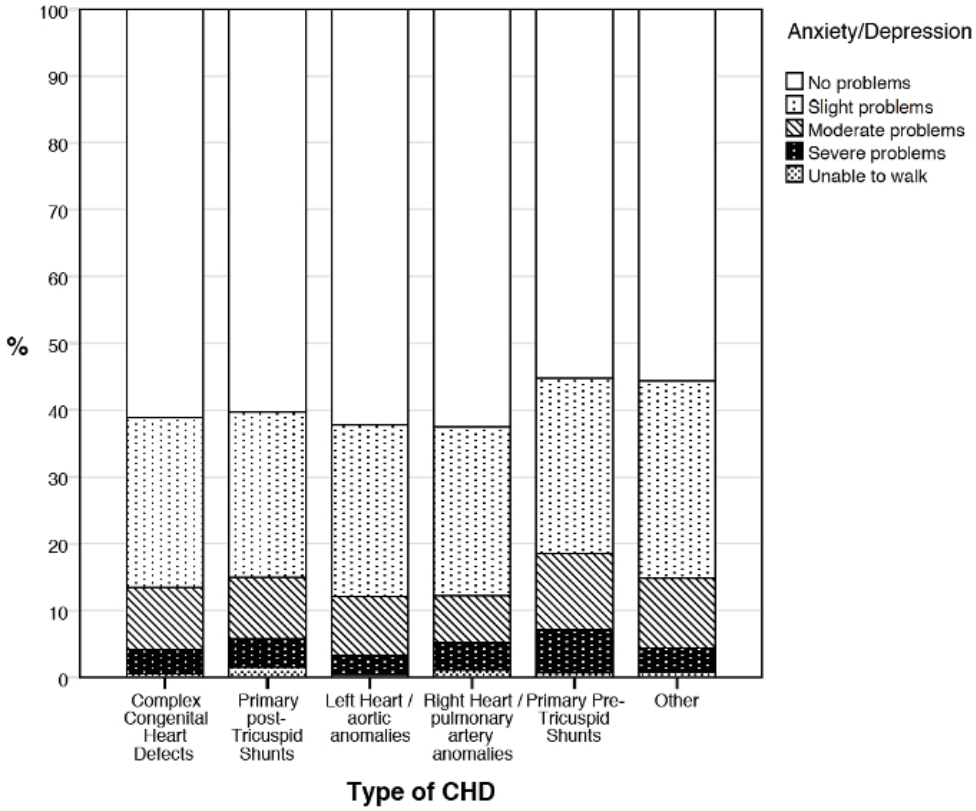

Figure 5: Distribution of scores for Anxiety/Depression

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4/5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4/5
		(*b*) Describe any methods used to examine subgroups and interactions	4/5
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	n/a

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The "Well-being paradox" revisited: A cross-sectional study of quality of life in over 4,000 adults with congenital heart disease

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The "Well-being paradox" revisited: A cross-sectional study of quality of life in over 4,000 adults with congenital heart disease

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Abstract

Objective: The present cross-sectional study investigated quality of life (QOL) in a large cohort of German adults with congenital heart disease (ACHD) in association with patient-related and clinical variables.

Design: Cross-sectional survey.

Participants: Between 2016 and 2019, a representative sample of 4,014 adults with various forms of CHD was retrospectively analyzed. Inclusion criteria were confirmed diagnosis of CHD, participant age 18 years and older, necessary physical, cognitive and language capabilities to complete self-report questionnaires.

Primary and secondary outcome measures: QOL was assessed using the EQ-5D-5L. Sociodemographic and medical information was obtained by a self-devised questionnaire. Associations of QOL with patient-reported clinical and sociodemographic variables were quantified using multiple regression analysis and multiple ordinal logit models.

Results: Overall, ACHD (41.8 ± 17.2 years; 46.5% female) reported a good QOL comparable to German population norms. The most frequently reported complaints occurred in the dimensions pain/discomfort (mean: 16.3, SD: $p<0.001$) and anxiety/depression (mean: 14.3, $p<0.001$). QOL differed significantly within ACHD subgroups, with patients affected by pre-tricuspid shunt lesions indicating the most significant impairments ($p<0.001$). Older age, female sex, medication intake and the presence of comorbidities, were associated with significant reductions in QOL ($p<0.001$). CHD severity was positively associated with QOL within the dimensions of self-care (odds ratio [OR] 0.148, 95% CI .04-.58) and mobility (odds ratio [OR] 0.384, 95% CI .19-.76).

Conclusion: Current findings temper widely held assumptions among clinicians and confirm that ACHD experience a generally good QOL. However, specific subgroups may require additional support to cope with disease-related challenges. The negative correlation of QOL with age is especially alarming as the population of ACHD is expected to grow older in the future.

Keywords: *adults with congenital heart disease; psychological situation; quality of life; prevention; EQ5D*

Strenghts and Limitations

- First study of its kind exploring quality of life (QOL) among 4,014 patients with different medical and patient-related backgrounds.
- Uniform conceptualization of QOL based on EQ-5D-5L, which is a highly reliable and valid outcome measure within the cardiovascular area.
- Present findings help clinicians to identify specific subsets of patients who require extra psychological support and therefore constitute a major step in paving the way towards integrative cardiac care.
- Causal inferences are not possible due to the cross-sectional design of this study.
- Ambiguous findings open new avenues for future research in understanding the construction of self-rated health despite or as a consequence of CHD.

Introduction

Congenital heart defects (CHD) are the most common isolated inborn organ malformations and affect 1.35–1.5 million children each year. Although 90% of patients with CHD survive into adulthood, many of them are not cured and need to adapt to their chronic medical condition throughout their lives [1]. Besides symptoms related to their heart disease, lifelong psychosocial impairments may seriously impact the patients´ perceived quality of life (QOL) [2]. While clinical research traditionally focused on objective medical outcomes, the relevance of QOL and various related patient-reported outcomes is increasingly recognized in the evaluation of care for adults with congenital heart disease (ACHD) [3].

Research on QOL in ACHD is still relatively scarce and not conclusive. Empirical findings indicate that QOL among ACHD is compromised by sociodemographic factors (unemployment, older age, single status), psychological features (negative illness perceptions, distressed personality) and medical characteristics (e.g. hospitalization, worse functional status). QOL has been found to be positively associated with higher socioeconomic and educational status, stronger social support, better functional class, better knowledge of CHD, stronger sense of coherence as well as the absence of cardiac surgery. Existing findings are inconsistent regarding cardiovascular status, medication, age, and gender, although these variables appeared to be the most frequently investigated determinants [4].

These inconsistent results of existing research on QOL in ACHD can be attributed to a lack of a clear conceptual background, inconsistent methods and insufficient sample sizes [4]. Additionally, the high heterogeneity of ACHD constitutes a substantial confounding factor due to their great anatomical and clinical disease complexity. Most studies on QOL in ACHD focused on specific subgroups of patients which limits their informational value. Consequently, clinical parameters were not sufficiently examined to explain potential differences in QOL by the underlying diagnosis or severity of CHD. Although a recent review attests temporal qualitative improvements in QOL studies over the last decades, the current research situation still fails to meet scientific quality criteria [5].

The present study aimed to assess QOL within a large sample of ACHD in Germany and examine potential determinants of QOL in terms of patient-related and medical characteristics. Identifying determinants of QOL along with special needs of ACHD could advance the improvement of health care for this growing patient population.

Methods

Design

The present study represents a sub-analysis of the nationwide VEMAH initiative (“Versorgungssituation von Erwachsenen mit angeborenen Herzfehlern”, engl. “Medical Care Situation of ACHD”). Detailed

information on the rationale, design, and methods is documented in a former published paper [6]. VEMAH is a multicenter, cross-sectional study to assess the health care situation of ACHD in Germany. Coordination of VEMAH was initiated and carried out by the German Heart Center Munich.

Population

A questionnaire package was consecutively addressed to ACHD presenting at the Department of Congenital Heart Disease and Pediatric Cardiology of the German Heart Center Munich and the Department of Cardiology of the University of Erlangen. Additionally, the health insurance provider "AOK Bayern" distributed questionnaires to their policyholders with CHD in Bavaria, and the "National Register for Congenital Heart Defects" in Berlin, Germany, invited its members to participate in the study online. Guidelines on good clinical practice and data protection guidelines were followed. Inclusion criteria were: (1) confirmed diagnosis of CHD according to the definition of Thiene & Frescura, [7] (2) participant age 18 years and older, (3) necessary physical, cognitive and language capabilities to complete self-report questionnaires.

Measures

Patients completed a questionnaire either in person, online or by mail. Data collection took place between 2016 and 2019. QOL was measured using the generic questionnaire EQ-5D-5L[8].

I. *Demographic and clinical information*

Sociodemographic and medical information was obtained by a self-devised questionnaire. Medical variables included leading CHD, medication, presence of cyanosis, (non-) cardiac comorbidities and hereditary diseases. Following the recommendations of the American College of Cardiology, patients were divided into three severity groups based on their CHD diagnosis (ACC) [9].

II. *Quality of Life (EQ-5D-5L)*

QOL was measured using the updated five-level version of the EQ-5D [8] which provides a simple, generic measure of a patient's perceived health status. The EQ-5D-5L consists of a descriptive system questionnaire and a visual analogue scale (VAS). The descriptive system compromises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each patient was asked to indicate his perceived impairments on a 5-point Likert scale ranging from "no problems" to "extreme problems/unable". Responses were converted into a single weighted index score (EQ-5D index) which indicates how good or poorthe respondent´s health status is based on existing population norms. A value set for the EQ-5D-5L, based on a representative sample of the German population, has recently been developed [10]. The VAS indicates a patient's overall health state on the day of the questionnaire completion. It is a scale which ranges from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine") and provides a quantitative measure of a patient's perceived health. The EQ-

5D-5L proved to be a reliable and valid method for measuring QOL in cardiovascular populations (Cronbach's alpha = 0.856) [11].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 (IBM, Armond, New York, United States). Descriptive measures were calculated for sample characteristics, including patient reported sociodemographic and medical variables (absolute and relative frequencies, mean and standard deviations). The relationships between CHD diagnosis groups and EQ-5D-index values, including the underlying dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression were analysed. The comparison of ordinally scaled values was based on cumulative frequencies representing the relative proportion of patients with moderate to severe symptoms on the specific dimensions. Kruskal-Wallis-tests were applied to reveal significant differences between EQ-5D-dimensions and metric index values. Furthermore, the relationship between both EQ-5D VAS scores and dedicated index values was analysed with respect to various patient characteristics. Multiple regression models using Ordinary least squares (OLS)-estimates were calculated, while bivariate Pearson-coefficients were used to analyse the correlation between VAS and index scores. Finally, multiple ordinal logit models were applied to identify significant predictors of the respective QOL dimensions. For all tests, the statistical significance level was set at $p < 0.05$. Data analysis was currently performed for complete cases on each variable. To rule out a potential distortion of findings, a further comparison between statistically included and excluded patients was conducted and revealed no significant differences concerning their QOL.

Patient and Public Involvement

Neither patients nor the public were involved in the design and conduct of this research. The methodology of this research was adapted in multidisciplinary collaboration.

Results

Sample characteristics

A total of 4,014 patients was analysed (46.5% female) (***Table 1).*** The mean age of ACHD was 41.8 ± 17.2 (18-97) years. Patients were subclassified according to the underlying CHD into six main groups, consisting of complex CHD (n=581); pre-tricuspid shunts (n=621); post-tricuspid shunts (n=406); right heart or pulmonary artery anomalies (n=526); left heart or aortic anomalies (n=898); and miscellaneous CHD (n=602). 15.4 % of patients (n=602) presented with cyanosis. The severity of CHD was determined according to the Warnes classification system as simple (n=1,722, 62.0%), intermediate (n=650, 23.4%) or severe (n=406, 14.6%) [12].

QOL and ACHD

EQ-5D dimensions were found to be differently associated with CHD subgroups. Significant differences between the underlying diagnosis were found on all dimensions (p<.001). Compared to all other subgroups, pre-tricuspid shunts were particularly impaired in mobility, daily activities, pain/discomfort and anxiety/depression (***Table 2***). In contrast, complex CHD showed the least problems on the respective descriptive dimensions (***Figure 1-5***).

Similar results were reflected by EQ-5D VAS and index values (p<.001) with EQ-5D VAS values being highest in patients with right heart/pulmonary artery anomalies and complex CHD and lowest in patients with pre-tricuspid shunts. Observed differences were less extreme between descriptive EQ-5D index values. Both EQ-5D values were positively correlated (r=.623, p<.001), with coefficients being the lowest for patients with complex CHD (r=.579, p<.001) and highest for patients with left heart/aortic anomalies (r=.653, p<.001). Variations in QOL were observed depending on the type of measurement which was applied. Accordingly, the mean VAS score displayed a significantly lower QOL than the descriptive EQ-5D index value.

Patient-related Determinants of QOL

OLS-Regression models were applied to analyse relationships of sociodemographic variables with EQ-5D VAS and index values (***Table 3)***. At the 5% level of significance, age had the highest negative impact on VAS values (β=-.32) and Index values (β=-.22). Thus, QOL decreased with advancing age. Patients aged 65+ years indicated the lowest values on both scales. Means for both EQ-values were slightly higher in male than in female patients. Medication intake had significant negative effects on QOL in both measures. Model fit was slightly higher for the dependent variable in VAS values (R^2=.190) than EQ-5D index values (R^2=.112).

CHD-related Determinants of QOL

EQ-5D-dimensions were analysed more specifically in regard to different medical features such as connective tissue disease diseases with cardiovascular involvement, cyanotic status and severity codes of CHD. Several ordered logistic regression models were applied using each of the five dimensions as dependent variables (***Table 4***). Generally, patients with comorbidities had significantly increased odds of reporting problems on all dimensions than patients without comorbidities (p<.05). Non-cardiac comorbidities accounted for significantly higher odds of having problems than cardiac comorbidities. No significant effects could be observed for cyanotic status. Furthermore, regression models showed no effects for patients with simple or moderate disease severity classes. Apparently,severely classified patients indicated decreased odds of suffering from issues related to mobility or self-care than patients in lower Warnes' classes.

Discussion

QOL is one of the most important measures used to assess the psychosocial impact of chronic disease on a patient's life. This is the first study to investigate patient reported QOL within a cohort of 4,014 patients encompassing a broad spectrum of CHD. QOL in ACHD was assessed by utilizing the EQ-5D-5L, a highly reliable and valid outcome measure within the cardiovascular area [13]. It compromises two types of measurement and therefore provides a global view on QOL in terms of general life satisfaction. This allowed to reveal genuine differences in QOL among patients with different medical and sociodemographic backgrounds, regardless of methodological considerations. Within the context of this study, QOL quantifies the influence of CHD on a patient's ability to function and derive personal satisfaction from life.

QOL in ACHD

In line with previous findings [14], ACHD in general reported a good level of wellbeing which is comparable to German population norms [15]. The two-fold measure of QOL revealed that the type of measurement affects QOL scores differently. Apparently, the overall VAS score indicated a significantly lower QOL than the descriptive EQ-5D index value. One explanation for this discrepancy are differences in the QOL coverage of both measures. It can be assumed that the descriptive system encourages a patient to examine QOL from various angles as the system breaks down QOL into various components. Thus, QOL is regarded as a subjective concept being influenced by multiple causal factors [16]. In contrast, VAS picks up a one-dimensional view of perceived health where patients may indicate a higher occurrence of problems by focusing on somatic health restrictions imposed by their CHD. When comparing the quantitative association of CHD with QOL to other chronic disorders, the average reduction in VAS values in the current sample roughly resembles observations of various other heart diseases [15]. In line with previous research, patients most frequently reported problems in the areas of pain/discomfort (16.3%) and anxiety/depression (14.3%) [17]. These rates lie considerably above German population standards, which document symptoms of anxiety/depression in 4.7% of the general public. This result further supports previous research showing that ACHD are specifically prone to increased psychological distress and therefore require additional psychosocial support [18].

A closer look at different diagnosis groups reveals, that patients with pre-tricuspid shunts were particularly impaired in QOL. Comparable data have previously documented that QOL is not necessarily congruent with the complexity or severity of a heart disease. Even mild primary pre-tricuspid shunts can have a considerable negative impact on QOL [19]. Clinical reality shows that pre-tricuspid shunts are often detected incidentally and later in life creating a different psychological situation than diagnosis of CHD early in life. Children, who grew up with the awareness of their CHD, may acquire a greater sense of appreciation for life and expectations consistent with their capabilities and limitations [20]. Qualitative research on ACHD indicates that patients perceive the awareness of their childhood condition as a ressource to re-evaluate life priorities and develop a new life perspective [21]. A recent

study has further established, that sense of coherence is a highly significant predictor of QOL in ACHD [22]. Based on theoretical considerations, SOC develops during childhood and is thought to be fully developed by the age of 30 years [23]. Patients who may be diagnosed later in life may have missed the chance to develop and refine coping mechanisms and may thereforeexperience the effects of their CHD more negatively leading to higher emotional distress. Life-stage variables, such as age at diagnosis or years of survival, need to be further investigated as possible determinants of QOL.

Socioeconomic determinants of QOL

Despite good overall QOL, EQ-5D index and VAS values deteriorated with increasing age. This might be explained by the uncertainty in disease prognosis manifesting itself in an increased sense of vulnerability in this patient group [24]. Most patients with CHD are known to do well in the first decades of life until they eventually develop unexpected age and disease-related comorbidities. This development deserves special attention as the group of ACHD is expected to grow steadily in the future [1].

In contrast to previous findings [14], the present study revealed modest gender-related differences in QOL. Females were more likely to report poor QOL than males. These findings may be attributed to psychosocial factors rather than gender per se [25]. In general, gender is found to influence health expectations, health behaviours and perceived health outcomes [26]. Females may face a triple burden shouldering family responsibility, professional ambition and demands of their chronic disease. Research has demonstrated that females were less likely to return to work, more likely to recline psychological counselling and more socially isolated than males [27]. It has also been argued that females were more willing to disclose problems than males concerning their QOL, which may partly explain the difference in their QOL [26]. Engelfriet et al. (2005) also showed that females with CHD were more often symptomatic and presented functional impairments, despite a higher overall mortality in males over a 5-year period [28]. Gender disparities in patient-provider communication and dissatisfaction with health care might be another reason for decreased QOL in females. They might have higher expectations and a stronger demand for more participatory encounters with their healthcare providers [25]. Improved recognition and understanding of these gender-specific differences and challenges among ACHD is vital to improve their cardiovascular health over the long-term.

Reported medication intake was inversely associated with QOL in the present study This appears plausible because extensive or inappropriate medication can lead to severe side effects and even higher morbidity which may considerably impair QOL [29]. Aside from incorrect pharmaceutical treatment, the daily intake of medication is a constant reminder of illness and may have a negative impact on life satisfaction. Consequently, medication may either be a facilitator by providing new opportunities or an intensifier of problems by adverse psychological and somatic side effects.

Clinical determinants of QOL

Despite all advances in cardiac care, many CHD patients are left with significant residua, sequels or complications from the underlying anomaly [9, 30]. The impact of comorbidities in ACHD is largely underestimated [31]. The current study indicates that the presence of comorbidities increases the risk of problems on all dimensions of the EQ-5D. It is conceivable that affected patients report a lower health status since they may experience serious restrictions in various life domains. As comorbidities become increasingly dominant with advancing age, they may also explain the recorded deterioration of QOL with age in the present sample.

It is remarkable that patients with a more complex CHD scored significantly better in QOL domains. Until now, research has failed to demonstrate a clear-cut correlation between disease complexity and QOL [4]. Although the present finding may seem counterintuitive at first, there are various possible explanations for a better QOL in the light of a chronic condition. Keyes' two continua model of mental health [32] provides an important framework for explaining why patients might experience a good QOL despite their CHD. Accordingly, mental health is a complex state resulting from an interplay of environmental and psychological factors that have a profound influence on one's subjective wellbeing. Keyes' model holds that mental health (sometimes referred to as mental wellbeing) and mental illness are orthogonally related phenomena and not two endpoints of one single continuum. Although the current state of research confirms elevated levels of mental illness among ACHD [18], this does not necessarily imply impaired mental wellbeing or decreased QOL among these patients. Furthermore, the disability paradox explains why individuals may perceive a high QOL despite serious limitations. Accordingly, QOL depends upon finding a balance in life and maintaining harmonious social relationships [33]. The characteristics associated with a severe CHD may potentially include favourable and compromising factors and thus explain both extremes of QOL in ACHD. Lastly, growing up with a CHD can lead to a so-called "response shift" in terms of redefining priorities in one's life [34]. It is perceivable that patients develop different values from those of healthy persons in the face of a life-threatening, chronic illness. In this context, Sprangers et. al (1999) proposed a theoretical model to clarify and predict changes in QOL as a result of various dispositional characteristics, a patient's health status and mechanisms to accommodate to these changes [35].

Despite the extensive power of the present study, current results should be interpreted with caution due to certain limitations. The study was retrospective and cross-sectional in nature and does not allow to disentangle any conclusions about the directionality of effects or the development of QOL over time. Since all information was based on patient-reported outcomes, medical data may have been classified incorrectly due to a patient's limited knowledge of his or her condition. Consequently, surgical status of patients could not be identified. Subsequently, it would be advisable to synchronize these data with medical records in order to disentangle the effects of empirical-medical observations on QOL. As the enrolment was voluntary, selection bias could not be excluded and may hamper representativeness. Further, this study was performed at a tertiary care center for ACHD which does not reflect the typical

population of CHD. Further doubts must be raised about whether the applied EQ-5D-5L provides an accurate tool to evaluate QOL among AHCD. Although the updated 5L version demonstrates superior performance compared to its predecessor, psychometric properties in terms of high ceiling effects and weak discriminatory power have previously been questioned [36]. It has further been shown that the choice of value set has an impact on EQ-5D scores [37]. Since the present study used a population-based value set to construct QOL estimates, we strongly encourage to re-evaluate current findings on the basis of experience-based value sets. Further, the inventory was administered in three different ways. However, measurement invariance across the survey methods was not tested and the equivalence across the survey methods remains questionable. Since the primary aim of this study was to assess clinical determinants of QOL, sociodemographic variables were not explicitly reviewed within the present analysis. Based on the German healthcare system, the depicted sociodemographic variables are crucial indicators of access to medical supply and were therefore separately analyzed. Given previously documented associations between sociodemographic factors and QOL, generalization of the conclusions and transmission to patients from differing socioeconomic conditions is debatable. The present survey assessed biological sex with a binary value. Given the increasing incidence of transgender and gender non-binary individuals and that large health disparities exist for this population [38], future research should increasingly expand measures of sex/gender to be trans inclusive. Finally, no control group was involved, and data could only be compared to published national EQ-5D studies.

Conclusion

The present study shows that ACHD experience – on aggregate – a good QOL which is indistinguishable from healthy individuals. Against expectation, patients with complex CHD scored higher on QOL. However, specific subgroups of patients indicate significant reductions in QOL and may require extra support in their care to cope with challenges associated with their underlying CHD. The negative correlation with age deserves particular attention as it could lead to a decrease in QOL with the growing median age of this patient population.

QOL is regarded as a central target in the treatment of chronically ill patients. This study supports the need to further assess and promote mental wellbeing in ACHD to safeguard surgical successes of the past decades which have ensured the survival of CHD patients into adulthood. Successful treatment implies not only an increased length of survival but also enhanced subjective wellbeing and QOL.

Declarations

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***Competing Interest*:** The authors have no conflicts of interest to declare.

***Ethics Approval*:** The study was part of the nationwide VEMAH project which was approved on 04/05/2016 by the ethical committee of the Technical University of Munich (157/16S).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: All authors consent to the publication of the manuscript in the Journal "Clinical Researcb in Cardiology".

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions:

(1) Conception and design: CA, HK, JB

(2) Administrative support: CA, SF, SA, PE, UG, JH, HK, LP, MW, RN, JB

(3) Collection and assembly of data: *CA, SF, SA, UG, MW*

(4) Data analysis and interpretation: CA; SF

(5) Manuscript writing: CA, JB

(6) Final approval of manuscript: CA, SF, SA, PE, UG, JH, HK, LP, MW, RN, JB

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Tables

Table 1. Characteristics of the underlying study population.

Variables	n (%)
Age group (n=3,903)	
18-34	1,663 (42.6)
35-64	1,733 (44.4)
65+	507 (13.0)
Gender (n=3,898)	
male	2,087 (53.5)
female	1,811 (46.5)
Residence (n=3,855)	
City	775 (20.1)
Town	590 (15.3)
Rural	2,490 (64.6)
Insurance (n=3,905)	
Public	3,679 (94.2)
Private	219 (5.6)
No Insurance	7 (.2)
Type of CHD (n=4,014)	
Complex Congenital Heart Defects	581 (14.5)
Primary Pre-Tricuspid Shunts	621 (15.5)
Primary post-Tricuspid Shunts	406 (10.1)
Right Heart / Pulmonary artery anomalies	526 (13.1)
Left Heart / Aortic anomalies	898 (22.4)
Miscellaneous CHD	602 (15.0)
Unclassifiable	380 (9.5)
Warnes Class (n=2,778)	
Simple	1,722 (62.0)
Moderate	650 (23.4)
Severe	406 (14.6)

Table 2. Leading diagnosis of CHD and EQ-5D-results.

EQ-5D	Total	Complex Congenital Heart Defects	Primary pre-tricuspid shunts	Primary post-tricuspid shunts	Right Heart / pulmonary artery anomalies	Left Heart / aortic anomalies	Unclassifiable	Miscellaneous	p-Value
Dimension	**n=4,014**	**n=581**	**n=621**	**n=406**	**n=526**	**n=898**	**n=380**	**n=602**	
Mobility	12.2	8.6	13.6	10.4	9.6	10.5	15.0	16.6	<.001*
Self-Care	3.5	2.0	3.0	2.3	3.2	3.5	4.4	5.4	.017*
Usual activities	13.2	13.7	13.5	11.2	12.6	11.1	14.1	16.8	<.001*
Pain/Discomfort	16.3	13.7	20.4	12.3	11.8	14.3	19.5	22.7	<.001*
Anxiety/Depression	14.3	14.8	17.5	14.2	12.6	12.0	14.4	15.5	.002*
EQ-5D VAS	**n=3,761**	**n=540**	**n=605**	**n=388**	**n=485**	**n=844**	**n=351**	**n=548**	<.001*
Mean	76.15	78.21	73.29	77.28	79.50	77.36	74.32	72.80	
SD	18.97	17.12	19.93	19.90	17.48	18.55	19.56	19.57	
EQ-5D Index	**n=3,690**	**n=540**	**n=583**	**n=383**	**n=489**	**n=828**	**n=344**	**n=523**	<.001*
Mean	.90	.92	.89	.91	.92	.91	.88	.87	
SD	.15	.14	.15	.14	.15	.14	.16	.18	

Notes: Data for EQ-5D-dimensions represent relative percentages of patients, who indicated moderate to severe problems with respect to each dimension. Significant differences were calculated using Kruskal-Wallis-tests for independent samples.

Table 3. Patient characteristics and their correspondence with EQ-5D VAS and index values.

	EQ-5D VAS				EQ-5D Index			
Variables	Mean	SD	ß	p	Mean	SD	ß	p
Age group			-.32	<.001*			-.22	<.001*
18-34	83.46	14.75			.94	.11		
35-64	73.44	18.99			.89	.15		
65+	62.23	20.83			.82	.21		
Sex			.01	<.001*			.04	.004
Female	76.11	19.07			.90	.15		
Male	76.55	18.85			.91	.14		
Residence			.02	.084			.03	.060
City	76.30	17.49			.90	.15		
Town	77.08	18.26			.90	.15		
Rural	76.01	19.46			.90	.15		
Medication			-.22	<.001*			-.19	<.001*
No	79.16	17.13			.92	.13		
Yes	65.17	20.69			.83	.20		

Notes: Multivariate analysis was performed using OLS-regression models with EQ-5D VAS and Index values as dependent variables.

Table 4. Impact of medical features with respect to EQ-5D-dimensions.

Variable	n	**Mobility** n=3,070	**Self-Care** n=3,073	**Usual activities** n=3,068	**Pain/discomfort** n=3,051	**Anxiety/depression** n=3,061
Comorbidities						
Cardiac Comorbidities	1,463	.302* (.25-.36)	.525* (.38-.73)	.348* (.29-.41)	.331* (.28 - .39)	.467* (.40-.54)
Non-Cardiac Comorbidities	819	.263* (.22-.32)	.281* (.20-.39)	.222* (.18-.27)	.311* (.26 - .37)	.243* (.20-.29)
Cyanosis						
Cyanotic	744	.904 (.49-1.68)	.396 (.12-1.26)	.880 (.50-1.56)	1.088 (.65 -1.82)	.850 (.51-1.41)
Acyanotic	2,176	1.452 (.70-3.02)	.774 (.20-3.04)	1.207 (.63-2.30)	1.011 (.58 -1.77)	.695 (.40-1.19)
Warnes class						
Simple	1,722	1.396 (.69 – 2.84)	.707 (.18 – 2.84)	1.109 (.60 – 2.06)	.984 (.57 – 1.69)	.739 (.44 – 1.24)
Moderate	650	.848 (.50 – 1.45)	.538 (.17 – 1.69)	.985 (.60 – 1.61)	.884 (.57 – 1.37)	.921 (.60 – 1.41)
Severe	406	.384* (.19 – .76)	.148* (.04 – .58)	.710 (.39 – 1.30)	.620 (.36 – 1.08)	.742 (.43 – 1.27)

Notes: Displayed are odds ratios, upper and lower bounds (95% CI) respectively which were obtained from several ordered logistic regressions using EQ-dimensions as dependent variable.
** $p < .05$*

Figures

Figure 1: Distribution of scores for Mobility

Figure 2: Distribution of scores for Self-Care

Figure 3: Distribution of scores for Usual Activities

Figure 4: Distribution of scores for Pain/Discomfort

Figure 5: Distribution of scores for Anxiety/Depression

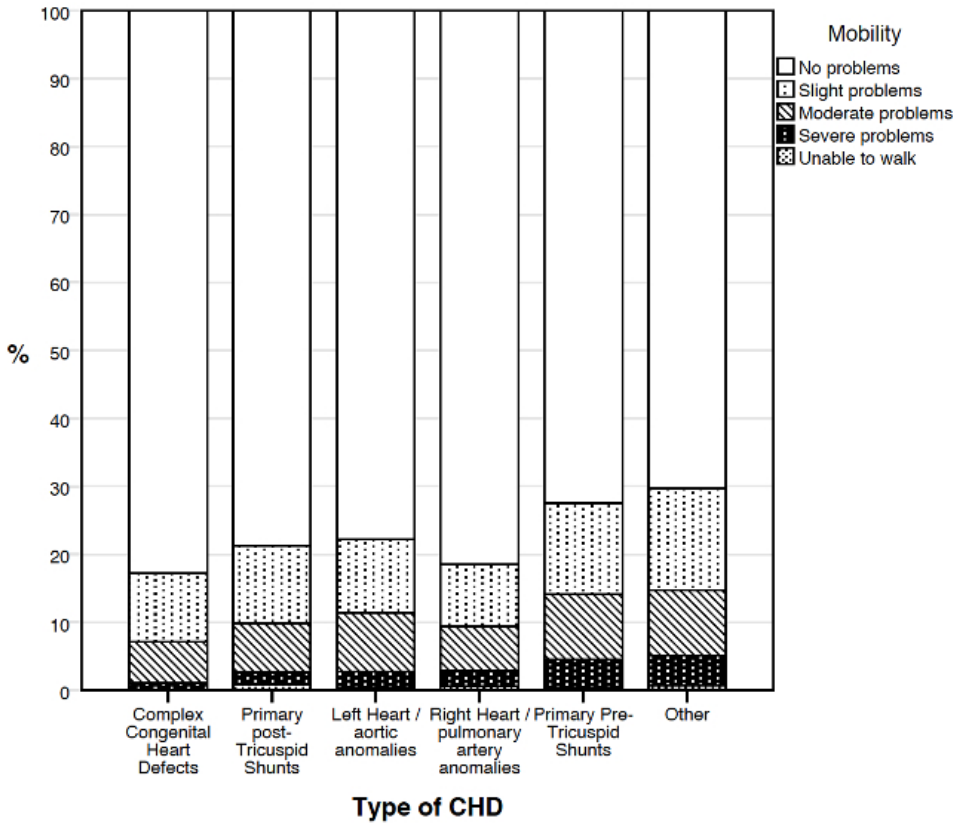

Figure 1: Distribution of scores for Mobility

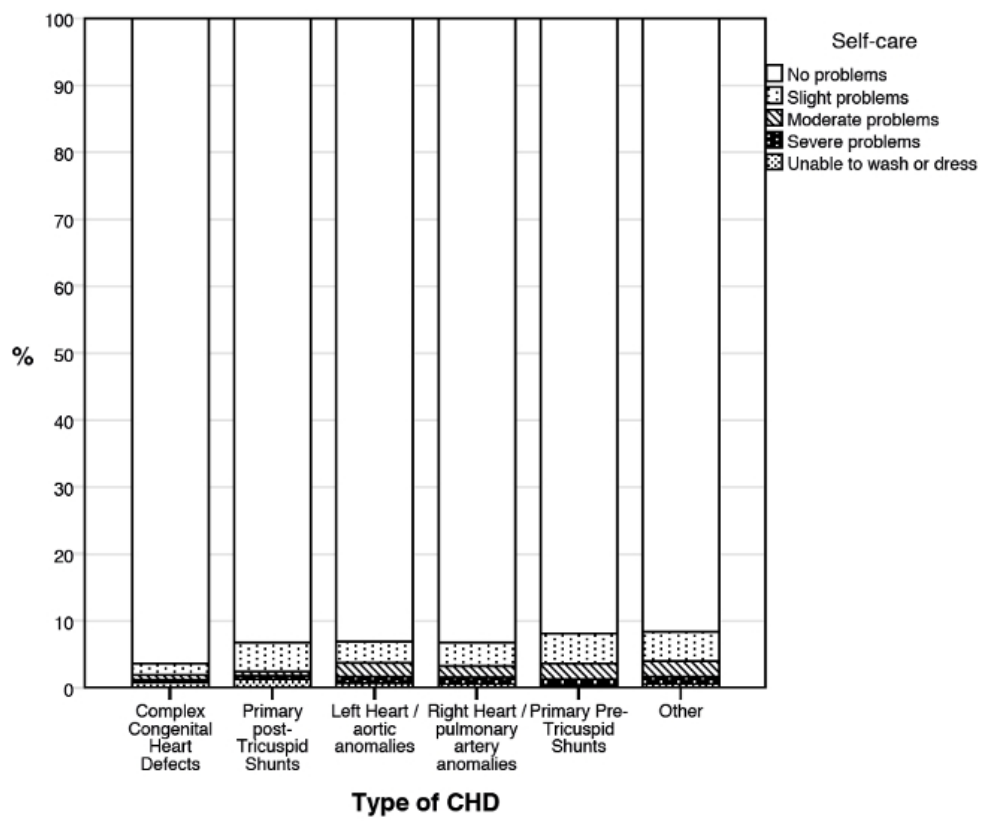

Figure 2: Distribution of scores for Self-Care

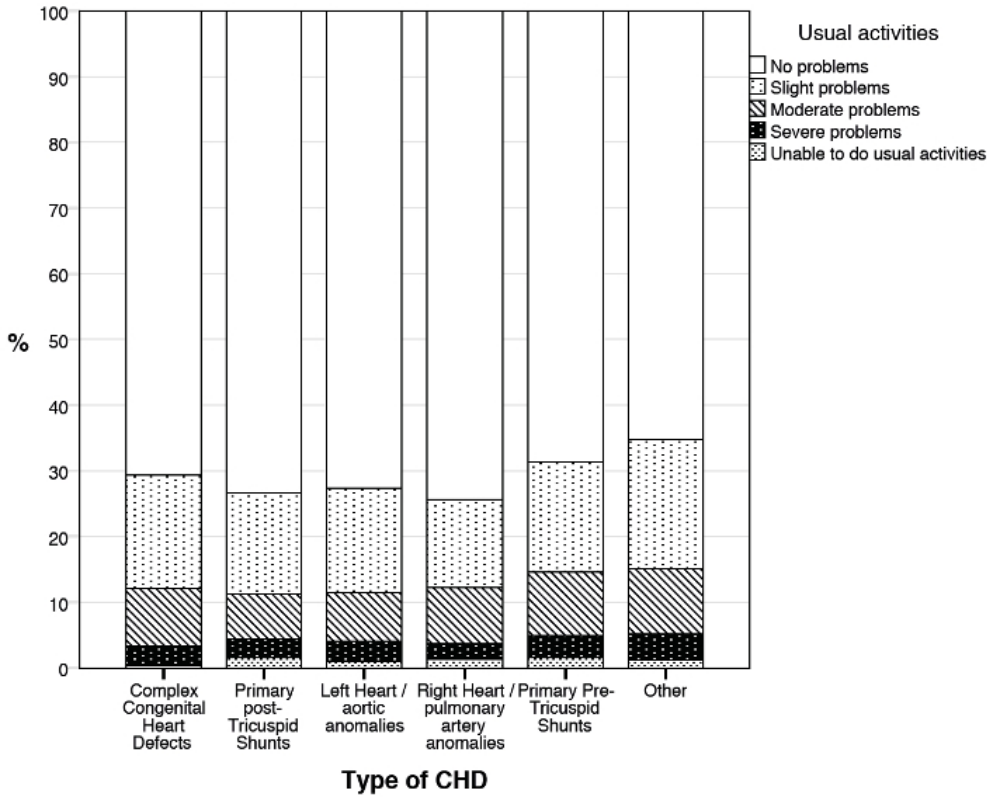

Figure 3: Distribution of scores for Usual Activities

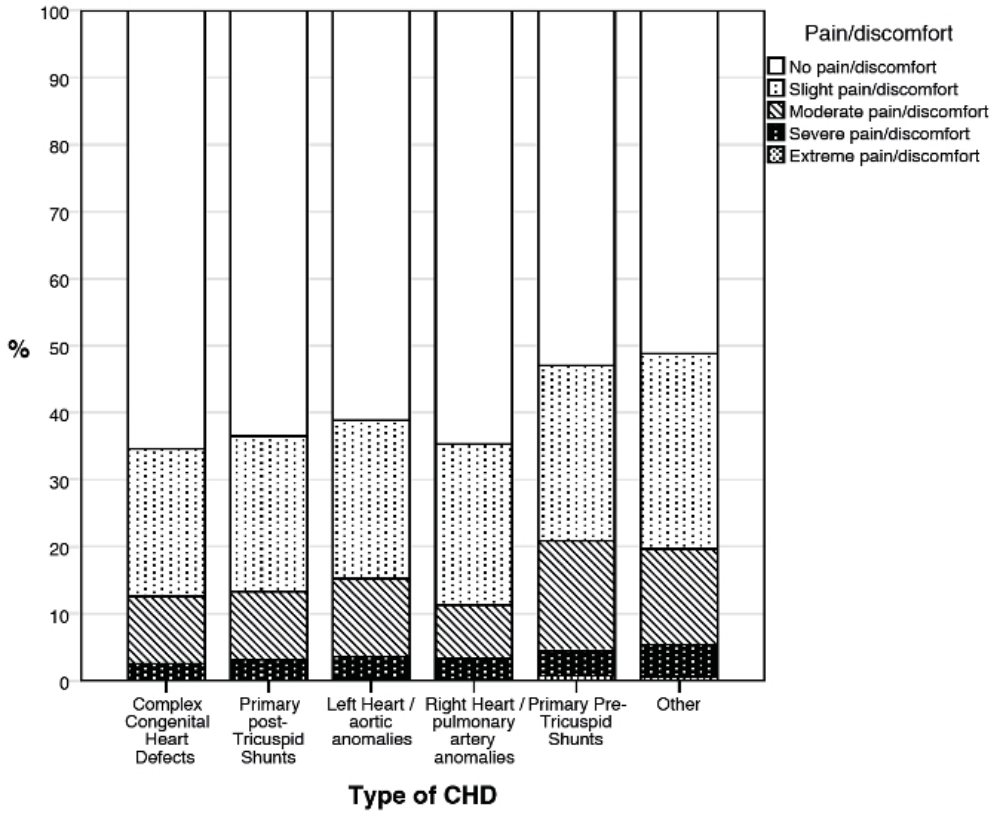

Figure 4: Distribution of scores for Pain/Discomfort

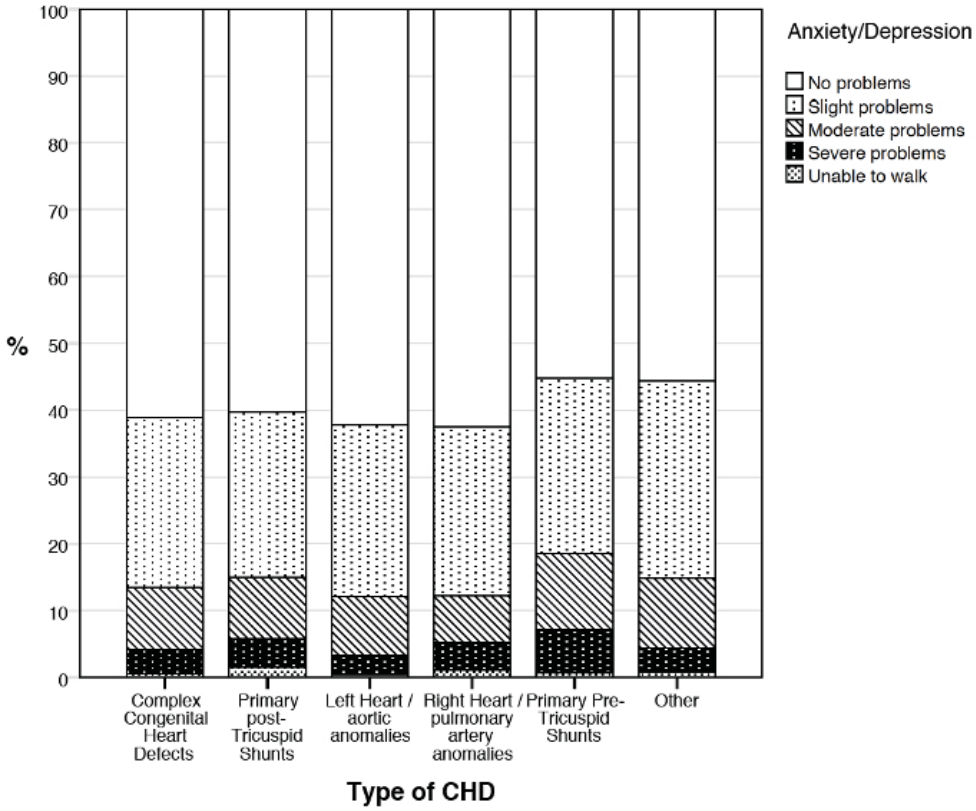

Figure 5: Distribution of scores for Anxiety/Depression

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4/5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4/5
		(*b*) Describe any methods used to examine subgroups and interactions	4/5
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	n/a

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.