PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The "Well-being paradox" revisited: A cross-sectional study of quality of life in over 4,000 adults with congenital heart disease
AUTHORS	Andonian, Caroline; Freilinger, Sebastian; Achenbach, Stephan; Ewert, Peter; Gundlach, Ulrike; Hoerer, Jürgen; Kaemmerer, Harald; Pieper, Lars; Weyand, Michael; Neidenbach, Rhoia; Beckmann, Jürgen

VERSION 1 – REVIEW

REVIEWER	caruso, rosario IRCCS Policlinico San Donato
REVIEW RETURNED	11-Mar-2021

GENERAL COMMENTS	Dear authors I found your manuscript interesting as it is informative about an under-investigated topic. Some minor points to improve the reporting: 1. In the method section, I suggest adding a subheading with the study design before describing the population 2. In the population paragraph, I do not understand the last sentence, “No patients were asked for input in the creation of this research” I suggest clarifying what you intended to report. 3. I suggest more focus on describing the procedure, maybe dedicating a sub-heading before stating the measures 4. The level of significance of the inferential analyses should be stated in the statistical analysis’s paragraph, not in the results (e.g., page 6, line 5). 5. As per my understanding, the data collection was based using multiple methods (online, paper-based forms). Although the EQ-5D-5L is a well-known tool, to the best of my knowledge, we do not have evidence showing the measurement invariance of different methods to collect data; for this reason, I suggest considering the multiple methods of data collection as a possible source of bias as no statistical tests were performed to assess the validity and reliability of the different approaches.

REVIEWER	Saarijärvi, Markus Goteborgs universitet Institutionen for vardvetenskap och halsa
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	Thank you for providing an interesting and valuable study. However, I do have several remarks and comments to further improve the present study. Major comments

The introduction of the methods section would benefit from a clear description of the design of the present study.

Page 4 – Line 7-9. Please provide response rates for the distributed questionnaire since this is lacking and is hampering the generalizability of the findings. Furthermore, were there differences in response rate between the questionnaires distributed in person, online or by mail? This is important to describe and can provide important guidance for future studies within this field of research.

Page 4 and 5 – Statistical analysis – Where there any missing data, and if so - how did you handle this in the analysis?

Page 4 – Line 11 – Please provide the self-devised questionnaire as a supplemental file as it is difficult to assess the relevance of the questionnaire and analyzed variables if not having the questions at hand. Furthermore, no description of the collected sociodemographic variables is provided in the methods. Furthermore, your included sociodemographic variables are weak, since you do not include income nor education level that are important predictors on QOL in patients with cardiovascular conditions. This also threatens the generalizability of your results since you claim that you have included patients with different sociodemographic background. Please add this to limitations.

Page 4 – Line 23-24 – Generally speaking, population based index scores are lower than experience based i.e., weights based on people with experience of a chronic condition, for instance the Swedish EQ5D weights (Burström et al 2014) . Please add more reflection/discussion on how the use of population based scores might have affected your results since your study sample consists of people living with chronic conditions where adaption to the condition plays a significant role. This is especially important since your findings indicate that patients with higher complexity scored better than those with lower complexities.

Further develop your methodological limitations/reflections with the following points:

- Although I agree that EQ5D is commonly used in cardiovascular research, it has many weaknesses in terms of discriminatory value and is today primarily used in health economic evaluations.
- Your choice of sociodemographic variables and how generalizable your results are since you did not include education level, employment status or income level
- The choice of having a binary value for gender, therefore excluding people who are non-binary or gender fluid.

Minor comments

Page 3 - Line 6 – I would in addition add that the relevance of patient reported outcome measures are increasingly recognized as well.

Page 4 – Line 3 – Please add a definition of CHD.

Page 4 – Line 4 – What is the difference between inclusion criteria 3 and 4 in terms of necessary language capabilities and German speaking? I would suggest remove inclusion criteria 4 since this is implicit from inclusion criteria 3.

Table 1 – Type of CHD. When calculating the 7 categories listed under type of CHD I get 4014 patients. Please check the numbers.

Page 5 – Line 19-20. A significant proportion of your sample was not classified according to the Warnes classification system, please provide more information on this.

Page 6 – Line 19-21. Your statement on that the results are remarkable is not appropriate for a results section. Please tone down this statement or move to discussion.

	Page 7 – Line 24-28 – Your statements on life-stage perspectives should include references to back this up. I suggest you should look into the extensive qualitative work performed in this area. Page 10 – Line 12 – Please clarify if the informed consent was written, oral or both to the participants.

VERSION 1 – AUTHOR RESPONSE

Comments to Reviewer 1 (Dr. Markus Saarijärvi):

Dear Dr. Saarijärvi,

We deeply appreciate your feedback and your revisions definitely gave impulse to further enhance the quality of our present manuscript. Please find our respective answers below:

Major Revisions

Comment 1: The introduction of the methods section would benefit from a clear description of the design of the present study.

Answer 1*: Thank you. We elaborated this section as follows (comp. page 3: line 28 – page 4: line 16):*

Study 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 (Neidenbach et al., 2021)). 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 (2) participant age 18 years and older, (3) necessary physical, cognitive and language capabilities to complete self-report questionnaires, (4) German speaking.

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 (German value set).

* Neidenbach, R., Achenbach, S., Andonian, C., Bauer, U. M., Ewert, P., Freilinger, S., ... & Kaemmerer, H. (2021). Systematic assessment of health care perception in adults with congenital heart disease in Germany.

Comment 2: Page 4 – Line 7-9. Please provide **response rates** for the distributed questionnaire since this is lacking and is hampering the generalizability of the findings. Furthermore, were there differences in response rate between the **questionnaires distributed in person, online or by mail?** This is important to describe and can provide important guidance for future studies within this field of research.

Answer 2: *Participants were recruited in several different ways: via personal invitation by their general practitioner, via postal invitation by the health insurance provider AOK Bayern, or via online/personal administration by the department of congenital heart disease and pediatric cardiology (German Heart Center Munich). Because of various recruiting modalities (online, postal, personal), it was not possible to determine a reference population who received an invitation to participate. Therefore, an overall response rate could not be calculated.*

Comment 3: Page 4 and 5 – Statistical analysis – Where there any **missing data**, and if so **-** how did you handle this in the analysis?

Answer 3: *Thank you for your legitimate remark. Indeed, missing data potentially present a problem in distorting findings. Because of the various sample sizes in different steps of the analysis, we have chosen not to conduct a general comparison between included and excluded patients. However, a comparison between statistically included and excluded patients concerning their QOL revealed no significant differences in relation to CHD subgroups and sex. Data analysis was therefore only performed for complete cases on each variable since this technique is particularly advantageous to samples with such a large volume of data without significantly distorting readings.*

Comment 4: Page 4 – Line 11 – Please provide the self-devised questionnaire as a supplemental file as it is difficult to assess the relevance of the questionnaire and analyzed variables if not having the questions at hand. Furthermore, no description of the collected sociodemographic variables is provided in the methods. Furthermore, your included sociodemographic variables are weak, since you do not include income nor education level that are important predictors on QOL in patients with cardiovascular conditions. This also threatens the generalizability of your results since you claim that you have included patients with different sociodemographic background. Please add this to limitations.

Answer 4: *Of course, we will provide the self-devised questionnaire as a supplemental file to this manuscript as it may have additional explanatory value on its own merits. Indeed, former research in ACHD (partly undertaken at our premises, see Vigl et al., 2013) has confirmed significant associations between QOL and sociodemographic variables among ACHD. This is why our primary aim was to examine differences in QOL in relation to numerous medical variables (leading CHD diagnosis, cyanotic status, non-/cardiac comorbidities, Warnes class, hereditary disease). After adjustment for sociodemographic and patient-related factors (age, gender, residence, insurance status, socio-economic group, employment), QOL appeared to be significantly associated with ACHD subgroups. We amended the manuscript accordingly (page 10: line 6-9).*

* Vigl, M., Niggemeyer, E., Hager, A., Schwedler, G., Kropf, S., & Bauer, U. (2011). The importance of socio-demographic factors for the quality of life of adults with congenital heart disease. *Quality of Life Research*, *20*(2), 169-177.

Comment 5: Page 4 – Line 23-24 – Generally speaking, population based index scores are lower than experience based i.e., weights based on people with experience of a chronic condition, for instance the Swedish EQ5D weights (Burström et al 2014). Please add more reflection/discussion on how the use of population-based scores might have affected your results since your study sample consists of people living with chronic conditions where adaption to the condition plays a significant role. This is especially important since your findings indicate that patients with higher complexity scored better than those with lower complexities.

Answer 5: *Thank you for this valuable input! Indeed, an experience-based value set (EBVS) for ACHD has been lacking until now. A recent study conducted by Leidl et al. (2017) proves that utility-based value sets (UBVS) rendered slightly higher values than EBVS for mild health states and clearly lower values once severe or extreme problems occur. Thus, the difference between EBVS and UBVS increased with increasing severity of health states. Based on that, the use of UBVS may hardly have affected our finding, that patients with higher complexity scored higher in QOL. However, specific subgroups who stood out as being particularly at risk for decreased QOL (higher age, female gender, medication intake, primary pretricuspid shunts) should definitely be re-evaluated on the basis of EBVS in future research. As a consequence of the current use of UBVS to construct QOL estimates, QOL enhancing interventions for these subgroups may potentially be overemphasized within the present study. Future research on EBVS in ACHD is needed to identify risk groups of patients that systematically differ in valuation. We amended the manuscript accordingly (page 10: line 1-4). A closer comparison between individual VAS scores and the population-based value set in relation to CHD subgroups will be conducted in a next step.*

*Leidl, R., & Reitmeir, P. (2017). An experience-based value set for the EQ-5D-5L in Germany. *Value in Health*, *20*(8), 1150-1156.

Comment 6: Further develop your methodological limitations/reflections with the following points:

6.1. Although I agree that EQ5D is commonly used in cardiovascular research, it has many weaknesses in terms of discriminatory value and is today primarily used in health economic evaluations.

6.2. Your choice of sociodemographic variables and how generalizable your results are since you did not include education level, employment status or income level

6.3. The choice of having a binary value for gender, therefore excluding people who are non-binary or gender fluid.

Answer 6: *Thank you for your remarks. We extended the "limitations" section accordingly (page 9: line 26 – page 10: line 15) .*

5.1. 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 (Feng et al., 2021). It has further been shown that the choice of value set has an impact on EQ-5D scores (Leidl et al., 2017). 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.

5.2 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.

5.3. 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 (Bauer et al., 2017), future research should increasingly expand measures of sex/gender to be trans inclusive.

*Feng, YS., Kohlmann, T., Janssen, M.F. *et al.* Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res* **30,** 647–673 (2021). https://doi.org/10.1007/s11136-020-02688-y.

Bauer, G. R., Braimoh, J., Scheim, A. I., & Dharma, C. (2017). Transgender-inclusive measures of sex/gender for population surveys: Mixed-methods evaluation and recommendations. *PloS one*, *12*(5), e0178043.

Minor comments

Comment 1: Page 3 - Line 6 – I would in addition add that the relevance of patient reported outcome measures are increasingly recognized as well.

Answer 1: *Manuscript was adapted accordingly (page 3: line 6).*

Comment 2: Page 4 – Line 3 – Please add a definition of CHD.

Answer 2: *Manuscript was adapted accordingly (page 3: line 1-2).*

Comment 3: Page 4 – Line 4 – What is the difference between inclusion criteria 3 and 4 in terms of necessary language capabilities and German speaking? I would suggest remove inclusion criteria 4 since this is implicit from inclusion criteria 3.

Answer 3: *Thank you. Criteria 4 was removed.*

Comment 4: Table 1 – Type of CHD. When calculating the 7 categories listed under type of CHD I get 4014 patients. Please check the numbers.

Answer 4: *Thank you for pointing that out. The manuscript was adjusted accordingly.*

Comment 5: Page 5 – Line 19-20. A significant proportion of your sample was not classified according to the Warnes classification system, please provide more information on this.

Answer 5: *Since this study relies on patient-reported information, inconsistent or unclear information was handled as missing outcome data and not retained for statistical analysis.*

Comment 6: – Line 19-21. Your statement on that the results are remarkable is not appropriate for a results section. Please tone down this statement or move to discussion.

Answer 6: *We agree. This phrase has been deleted.*

Comment 7: Page 7 – Line 24-28 – Your statements on life-stage perspectives should include references to back this up. I suggest you should look into the extensive qualitative work performed in this area.

Answer 7: *To our knowledge, there is currently no evidence available on the psychological impact of an individual's age of onset of a chronic condition. However, qualitative research has shown that illness uncertainty is a central theme in the lives of ACHD (Moreland et al., 2018). The majority of these patients perceive the awareness of their childhood condition as a resource to re-evaluate life priorities and develop a new life perspective. A recent quantitative study has further established, that sense of coherence is a highly significant predictor of QOL in ACHD (Moons et al., 2021). Based on theoretical considerations, SOC develops during childhood and is thought to be fully developed by the age of 30 years (Antonovsky, 1987). Patients who may be diagnosed later in life may have missed the chance to develop and refine mechanisms to cope their CHD. We will certainly implement further information into the manuscript (page 7: line 32 – page 8: line 2).*

*Moreland, P., & Santacroce, S. J. (2018). Illness Uncertainty and Posttraumatic Stress in Young Adults With Congenital Heart Disease. *The Journal of cardiovascular nursing*, *33*(4), 356–362.

Moons, P., Apers, S., Kovacs, A. H., Thomet, C., Budts, W., Enomoto, J., ... & APPROACH-IS consortium and the International Society for Adult Congenital Heart Disease (ISACHD). (2021). Sense of coherence in adults with congenital heart disease in 15 countries: Patient characteristics, cultural dimensions and quality of life. *European Journal of Cardiovascular Nursing*, *20*(1), 48-55.

Antonovsky A. Unraveling the mystery of health: how people manage stress and stay well. San Fransisco' Jossey-Bass; 1987.

Comment 8: Page 10 – Line 12 – Please clarify if the informed consent was written, oral or both to the participants.

Answer 8: *Informed consent was obtained in written form.*

II. Comments to Reviewer 2 (Dr. Rosario Caruso):

Dear Dr. Caruso,

We very much appreciate your valuable feedback and made considerable effort to implement your suggested revisions! Please find our answers below:

Comment 1: In the method section, I suggest adding a subheading with the study design before describing the population.

Answer 1: *Thank you for this remark. We revised the method section accordingly (page 3: line 31 – page 4: line 3).*

Comment 2: In the population paragraph, I do not understand the last sentence, “No patients were asked for input in the creation of this research” I suggest clarifying what you intended to report.

Answer 2: *Acknowledged. We reformulated the required patient involvement statement within the methods section of the present manuscript (page 5: line 18-20).*

Comment 3: I suggest more focus on describing the procedure, maybe dedicating a sub-heading before stating the measures

Answer 3: *Thank you. Based on your remark, we elaborated this section as follows (page 3: line 31 – page 4: line 14):*

Study 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 (Neidenbach et al., 2021)). 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.

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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].

* Neidenbach, R., Achenbach, S., Andonian, C., Bauer, U. M., Ewert, P., Freilinger, S., ... & Kaemmerer, H. (2021). Systematic assessment of health care perception in adults with congenital heart disease in Germany.

Comment 4: The level of significance of the inferential analyses should be stated in the statistical analysis's paragraph, not in the results (e.g., page 6, line 5).

Answer 4: *Indeed. We included the following phrase into the statistical analysis section: For all statistical tests, a p-level < 0.05 was considered significant (page 5: line 16)*

Comment 5: As per my understanding, the data collection was based using multiple methods (online, paper-based forms). Although the EQ-5D-5L is a well-known tool, to the best of my knowledge, we do not have evidence showing **the measurement invariance of different methods to collect data;** for this reason, I suggest considering the multiple methods of data collection as a possible source of bias as no statistical tests were performed to assess the validity and reliability of the different approaches.

Answer 5: *Thank you for noting that. We extended the "limitations" section accordingly (page 10: line 4-6).*

"Within the present study, our 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."

VERSION 2 – REVIEW

REVIEWER	caruso, Rosario IRCCS Policlinico San Donato
REVIEW RETURNED	28-Apr-2021

GENERAL COMMENTS	Dear Authors, I found my comments properly addressed in the amended version of the manuscript.

REVIEWER	Saarijärvi, Markus Goteborgs universitet Institutionen for vardvetenskap och halsa
REVIEW RETURNED	07-May-2021

GENERAL COMMENTS	Thank you for your responses and corrections to your manuscript. My only remaining comment is regarding your response to comment 3. Comment 3: 4 and 5 – Statistical analysis – Where there any missing data, and if so - how did you handle this in the analysis? Answer 3: Thank you for your legitimate remark. Indeed, missing data potentially present a problem in distorting findings. Because of the various sample sizes in different steps of the analysis, we have chosen not to conduct a general comparison between included and excluded patients. However, a comparison between statistically included and excluded patients concerning their QOL revealed no significant differences in relation to CHD subgroups and sex. Data analysis was therefore only performed for complete cases on each variable since this technique is particularly advantageous to samples with such a large volume of data without significantly distorting readigs. COMMENT ON YOUR ANSWER: Please add a comment on this performed comparison and that you performed the analysis only on complete cases in the analysis section in the methods.

VERSION 2 – AUTHOR RESPONSE

Comments to Reviewer 1 (Dr. Markus Saarijärvi):

Comment 1: Thank you for your responses and corrections to your manuscript. My only remaining comment is regarding your response to comment 3.
Comment 3: 4 and 5 – Statistical analysis – Were there any missing data, and if so - how did you handle this in the analysis? Please add a comment on this performed comparison and that you performed the analysis only on complete cases in the analysis section in the methods.

Answer 1: Thank you. We amended the manuscript accordingly (page 5, l. 15-18)

> *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.*

Comments to Reviewer 2 (Dr. Rosario Caruso):

Comment 2: Dear Authors, I found my comments properly addressed in the amended version of the manuscript.

Answer 2: We deeply appreciate your feedback, thank you.