Frailty and cognitive function in middle-aged and older adults with congenital heart disease

Frailty and Cognitive Function in Middle-Aged and Older Adults with Congenital Heart Disease

Running Title: Frailty and cognition in congenital heart disease

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Funding:

This work was funded by KU Leuven – University of Leuven, Research Foundation Flanders through grants 1159522N and 12E9819N, Swedish Heart and Lung Foundation through grant #20190525, UnIC (Unidade de Investigação Cardiovascular of FMUP) supported the costs of the translations into Portuguese used in Portugal, Children's Heart Unit Fund (www.chuf.org.uk), Newcastle upon Tyne through their funding of the CHUF Fontan nurse specialist, The Taiwan Cardiac Children's Foundation (http://www.ccft.org.tw/), Greta and Johan Kock's foundations, Regional research support Southern healthcare region, Skane University Hospital funds. The study was partially supported by Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato.

Disclosures: None

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Short tweet summarizing paper:

Half of adults with congenital heart disease are (pre-)frail, 40% face cognitive issues. Age, sex, comorbidities are predictor variables. #HeartHealth #CHD

Acknowledgements:

We are grateful to APPROACH-IS II participants who chose to take part in this research. We are also appreciative of researchers and support staff at participating centers who contributed to the study. The use of a large language model has greatly assisted us in rephrasing and ensuring the clarity and effectiveness of our language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Abstract:

Background: Life expectancy of patients with congenital heart disease (CHD) has increased rapidly, resulting in a growing and aging population. Recent studies showed that older people with CHD have a higher morbidity, healthcare utilization, and mortality. To maintain longevity and quality of life, understanding their evolving medical and psychosocial challenges is essential.

Objectives: We describe the frailty and cognitive profile of middle-aged and older adults with CHD, to identify predictor variables, and to explore the relationship with hospital admissions and outpatient visits.

Methods: Using a cross-sectional, multicentric design, we included 814 patients aged ≥ 40 years from 11 countries. Frailty phenotype was determined using the Fried method. Cognitive function was assessed by the Montréal Cognitive Assessment.

Results: In this sample, 52.3% of patients were assessed as robust, 41.9% as pre-frail, and 5.8% as frail; 38.8% had cognitive dysfunction. Multinomial regression showed that frailty was associated with older age, female sex, higher physiological class, and comorbidities. Counterintuitively, patients with mild heart defects were more likely than those with complex lesions to be pre-frail. Patients from middle-income countries displayed more pre-frailty than those from higher-income countries. Logistic regression demonstrated that cognitive dysfunction was related to older age, comorbidities, and lower country-level income.

Conclusion: Approximately half of included patients were (pre-)frail and over one-third experienced cognitive impairment. Frailty and cognitive dysfunction were identified in mild CHD patients, indicating that these concerns extend beyond severe CHD. Assessing frailty and cognition routinely could offer valuable insights into this aging population.

Condensed abstract:

In this international study of 814 adults with congenital heart disease (CHD), approximately 50% of patients were (pre-)frail, and nearly 40% experienced some degree of cognitive impairment. Frailty was associated with older age, female sex, worse physiological stage, and more comorbidities. Cognitive dysfunction was linked to increased age and more comorbidities. Frailty and cognitive dysfunction were observed in patients with mild heart lesions, indicating their presence goes beyond complex CHD. Assessing frailty and cognition routinely could offer valuable insights into the aging CHD population.

Keywords: Aging; Cognition; Frailty; Frailty phenotype, Heart defects, congenital

Abbreviations:

APPROACH-IS	Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study
CHD	Congenital Heart Disease
ACHD AP Classification	Adult Congenital Heart Disease Anatomic and Physiological Classification
MoCA	Montréal Cognitive Assessment
CCI	Charlson Comorbidity Index

INTRODUCTION

Congenital heart disease (CHD) is the most prevalent birth defect worldwide, occurring in almost 1 in 100 newborns [1]. While the life expectancy for these patients was limited five decades ago, now 90% of children with CHD, reach adulthood due to improved medical, surgical, and technical innovations [2]. This results in a substantially growing and aging population in which the number of adults exceeds the number of children in higher-income countries [2,3]. By 2030, it is estimated that 11% of the adult CHD population will be aged 60 years or older [4].

However, these successes in life expectancy come at a cost. As the survival rates of patients with CHD improve, the demand for adult CHD services grows [5]. Indeed, older patients with CHD exhibit a higher prevalence of morbidity, healthcare utilization, and mortality rates [5,6]. Understanding their evolving medical and psychosocial challenges is vital for mapping their specific healthcare needs and maintaining longevity and quality of life [6,7]. Yet, limited information is available about the profile of the aging CHD population.

Several age-related morbidities, including coronary heart disease, heart failure, stroke, erectile dysfunction, diabetes, dementia, or cancer, occur earlier and more often in people with CHD compared to the general population [8]. This decrease in physiological capacity across multiple organ systems may be approximated to frailty. Frailty is defined as a decline in functional reserve, resistance, and resilience of multiple organ systems, leading to an accelerated functional decline and adverse health outcomes following stressor events [8,9]. The Fried frailty phenotype refers to a clinical syndrome that classifies patients as non-frail, pre-frail, or frail, based on five criteria: weakness, slow walking speed, unintentional weight loss, exhaustion, and low physical activity [10]. Growing evidence suggests that frailty phenotypes can guide risk prediction in chronically ill patients, independent of age and comorbidity [11].

However, to our knowledge, the prevalence of frailty and the proportion of the Fried frailty phenotypes have not been comprehensively investigated in older patients with CHD.

A second important factor influencing the clinical profile of older patients with CHD is cognitive impairment. It is well-established that children with (complex) CHD are at risk for neurodevelopmental impairment [12-14]. Consequently, the American Heart Association issued guidelines for periodic neurocognitive assessment in children with CHD [13]. The causes of these deficits are multifactorial, interactive, and complex, including hypoxic/ischemic injuries caused by the condition and a spectrum of genetic, prenatal, pre-and postoperative risks. Medical and surgical therapies and resulting hypoperfusion also contribute to the development of neurological impairment. The prevalence and degree of neurodevelopmental deficits and disorders increase in correspondence with increasing CHD complexity [13,15-17]. More recently, there has been increased empirical investigation into the cognitive profile of adults with CHD. Despite the persistence of neurodevelopmental challenges into adulthood, there are also adult-onset risk factors for neurocognitive impairment [15,18-21]. Understanding the cognitive functioning of older patients with CHD is essential since impairment may adversely affect their quality of life, healthcare needs and mortality [15,22].

It is important to consider whether frailty and cognitive impairment are impacted by socio-economic factors. Frailty occurs more often in low- and middle-income countries than in high-income countries [23]. Because data on frailty and cognitive functioning in CHD are currently limited and because international studies covering countries from different income classes are imperative to yield generalizable findings, the present study aimed (i) to assess frailty and cognitive impairment in an international sample of middle-aged and older adults with CHD, (ii) to evaluate whether patient-related factors and country income level are predictor variables for frailty and cognition, and (iii) to explore consequences in terms of hospital admissions and outpatient visits.

METHODS

Study design

This study was part of the Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study II (APPROACH-IS II), with a cross-sectional global multicentric design [24]. This is a follow-up study to the initial successful international APPROACH-IS collaboration [25]. For this sub-study, focussing on frailty and cognitive impairment, patients were enrolled from 17 centers in 11 countries categorized as high-income (Belgium, Denmark, France, Italy, Portugal, South Korea, Sweden, Taiwan, and the United Kingdom) or upper-middle-income (Brazil and Bulgaria). The rationale and methodology of this study can be found in the published APPROACH-IS II methods paper [24].

Study population

Participants were eligible if they met the following criteria: (i) diagnosed with CHD; (ii) aged 40 years or older at study entry; (iii) diagnosed with CHD before the age of 10; (iv) receiving care at an adult CHD center; and (v) demonstrating the physical, cognitive and language capabilities required to complete self-report questionnaires and study tasks. Participating centers were encouraged to recruit 20 adults in each of the following age groups: (i) 40–50 years; (ii) 51–60 years; and (iii) older than 60 years.

Study procedure

Data were collected from August 1, 2019, until November 31, 2022. The original data collection period was extended due to pauses during the acute waves of the COVID-19 pandemic. Participants recieved unique study numbers, and their data were encoded in the Research Electronic Data Capture (REDCap) data management platform (Vanderbilt University, Nashville, TN, USA) [26].

Eligible patients were consecutively enrolled and seen at the outpatient clinic for adults with CHD. They were informed about the study's aim and procedure, and subsequently, verbal and written informed consent was obtained. A data collection officer/research assistant conducted cognitive and frailty assessments, in addition to gathering demographic and comorbidity data.

The Institutional Review Board of the University Hospital Leuven/KU Leuven (coordinating center) and the respective local institutional review boards of the participating centers approved the study. The research was conducted in accordance with the declaration of Helsinki [27]. The protocol was registered at ClinicalTrials.gov (NCT04902768).

Variables and instruments

Demographic data were collected through self-report questionnaires completed by patients, while medical data (e.g., CHD diagnosis, number of catheter interventions, number of cardiac surgeries, hospital admissions for cardiac reasons of at least one day over the past five years, and cardiac outpatient clinic visits over the past five years) were abstracted from medical records. Moreover, the Adult Congenital Heart Disease Anatomic and Physiological (ACHD AP) classification, incorporating both anatomical and physiological factors, was recorded [28]. The incorporated physiological factors encompassed the NYHA functional class; history of arrhythmias; cyanosis or hypoxemia; ventricular dilatation; ventricular dysfunction; aortic dilatation; pulmonary hypertension or Eisenmenger syndrome; venous stenosis/obstruction; arterial stenosis/obstruction; intracardiac shunt; and organ dysfunction [28].

Frailty phenotype was determined using the Fried method, which classifies patients as robust, pre-frail, or frail based on five criteria: self-reported unintentional weight loss, exhaustion, and physical activity; assessment of muscle weakness using a handgrip dynamometer (stratified by gender and BMI); and the performance of a 4.5m walking speed

test (stratified by gender and height) [10]. Participants were considered frail if they met 3 or more of the 5 criteria, pre-frail if they fulfilled 1 or 2 criteria, and robust if none of the criteria were present. The Fried method is commonly used and validated for frailty assessment in general populations and patients with chronic conditions [29,30].

Cognitive functioning was assessed using the Montréal Cognitive Assessment (MoCA), which evaluates multiple cognitive domains, including visuo-spatial skills, executive functions, attention, concentration, memory, language, abstraction, calculation, and orientation [31]. The MoCA is a well-established instrument with demonstrated validity in the CHD population [16]. The maximum MoCA score is 30 points; individuals with 12 years or less of formal education receive an extra point in addition to their earned score. A final score of 26 or higher indicates normal cognitive functioning.

To gain insight into the presence and burden of comorbidities, the Charlson Comorbidity Index (CCI) was calculated based on data collected from medical records [32]. As needed, collateral information was obtained directly from patients. Patients were classified into four categories: no comorbidities (score of 0), mild comorbidities (score of 1 to 3), moderate comorbidities (score of 4 to 7), or severe comorbidities (score of 8 or more).

Country-level income class was determined based on the World Bank's categorization of the Gross National Income (GNI): high-income (GNI≥ US$ 13,846), upper-middle-income (GNI US$ 4,466-13,845), lower-middle-income (GNI US$ 1,136-4,465) and low-income (GNI ≤ US$ 1,135) [33].

Statistical analysis

Data analysis was performed using IBM SPSS Statistics, version 29 (IBM Corp., Armonk, NY, USA). Normality and homogeneity were checked using the Shapiro-Wilk and Levene's tests. Data are presented as mean ± standard deviation (SD), median and interquartile range (IQR),

absolute numbers (n), percentages (%), odds ratios (OR), and 95% confidence intervals (95% CI). Spearman's rho test was used for correlation analysis. The relationships between frailty and sex, age, CHD complexity, physiological stage (i.e., ACHD AP classification), number of catheter interventions, number of cardiac surgeries, CCI (continuous), and World Bank Income Class were examined using a multivariable multinomial regression analysis. These predictor variables were also studied in relation to the MoCA score using multivariable logistic regression analysis. CCI unadjusted for age was used, to avoid the inflation effect of age. A negative binomial regression analysis was performed examining the potential association between frailty or cognitive function, and the number of hospital admissions and outpatient visits, corrected for age, sex, comorbidity, CHD complexity, and physiological component of the ACHD AP classification. The null hypothesis was rejected for p-values <0.05.

RESULTS

Sample characteristics

A total of 814 patients were included, with a median age of 52.0 years. Among them, 355 patients were aged 40-50 years (43.7%), 239 were aged 51-60 years (29.4%), and 218 were 60 years or older (26.9%). The sample consisted of 51.5% women. Most patients had CHD of moderate complexity (70.1%). In the past five years, most patients (50.7%) had 1 to 5 cardiac outpatient visits (mean: 7.8, SD: 8.1). Additionally, almost half of the sample (47.4%) had at least one cardiac admission the past five years (mean: 1.3, SD: 3.9). The demographic and clinical characteristics of the sample are presented in Table 1. The frequency distribution of heart defects are described in Supplementary Table 1.

PLEASE INSERT TABLE 1 ABOUT HERE

Frailty and cognitive functioning

Exhaustion was the most prevalent frailty criteria, occurring in 26.5% of the patients, followed by poor handgrip strength (15.6%) (Table 2). The other criteria occurred in about 10% of the patients. When determining the frailty phenotype, 52.3% of patients were robust, 41.9% were pre-frail, and 5.8% were frail (Table 3). The prevalence of frailty was 3.3% in patients aged 40-49, 4.9% in patients aged 50-59, and 10.4% in those aged 60 or older. It was found in 8.2% of women and 3.3% of men. Counterintuitively, patients with mild CHD were less often robust (40.8%) than patients with moderate (54.4%) or complex heart defects (52.2%). Regarding physiological stage, patients in stage C or D were frail in 6.1% and 16.7% of the cases, whereas 1.6% of patients in stage A or B were frail. Most patients with severe comorbidities (66.7%) presented with a frailty status. Patients from the two upper-middle-income countries were pre-frail in 52.7% of the cases and frail in 9.5%, while this was 40.8% and 5.4% in high-income countries, respectively (Table 3).

The median MoCA score was 27 (IQR: 24-29). The score distribution is given in Supplementary Figure 1. The different MoCA item scores can be found in Table 2. Using the established cutoff of 26, 38.8% of the patients displayed cognitive dysfunction (Table 3). Among patients aged 60 or older, 53.3% displayed some degree of cognitive dysfunction. Surprisingly, cognitive dysfunction occurred less often in patients with complex heart lesions (32.1%). However, as expected, it was the highest in patients of physiological stage D and in those with more comorbidities (Table 3). A weak negative correlation was found between being frail and cognitive function (ρ=-0.210, p<0.001). The frequency distribution of frailty versus cognitive function is provided in Supplementary Table 2, demonstrating a certain, albeit limited, coexistence of frailty and cognitive dysfunction.

PLEASE INSERT TABLE 2 AND 3 ABOUT HERE

Predictor variables of frailty and cognitive dysfunction

Multivariable multinomial regression analysis showed that older age, female sex, higher physiological stage, and more comorbidities were associated with a higher likelihood of having a pre-frail or frail status (Table 4). Patients with mild heart defects , a higher number of catheter interventions, and those from middle-income countries were more likely to be pre-frail than robust. The multinomial regression model explained 18.9% of the variance in frailty.

Multivariable logistic regression analysis demonstrated that cognitive dysfunction was related to older age, higher number of comorbidities and lower country income class (Table 4).

PLEASE INSERT TABLE 4 ABOUT HERE

Consequences of frailty and cognitive dysfunction

The number of outpatient visits in the preceding five years were associated with a better cognitive status (OR=1.024; 95%CI 1.010-1.038; p=0.001), when adjusted for age, sex, comorbidity, CHD complexity, and physiological component of the ACHD AP classification. Adjusted for these covariates, outpatient visits were unrelated to the number of cardiac admissions (OR=1.030; 95%CI 0.995-1.066; p=0.092). Frailty status was not associated with the number of cardiac outpatient visits in the previous five years (OR=1.070; 95%CI 0.971-1.179; p=0.173) or the number of cardiac admissions (OR=0.972; 95%CI 0.786-1.201; p=0.791), adjusted for the covariates mentioned above.

DISCUSSION

Understanding the evolving medical and psychosocial challenges of the growing aging population of patients with CHD is important to optimize their care, improve quality of life, and allocate health resources. This study assessed the frailty phenotype and cognitive

impairment of older adults with CHD, and the association with healthcare usage. An overview of the findings can be found in the Central illustration.

Frailty in patients with CHD

Almost half of the patients enrolled in this study were classified as pre-frail or frail. This prevalence is comparable to non-CHD community-dwelling older individuals [34]. However, individuals included in community frailty studies are typically 65 years of age or older, while in this study the median age was 52 years. Few studies have investigated frailty in people in their 40s and 50s, one of which also used the Fried phenotype [35,36]. Gordon et al. found frailty rates of 1.4% for people aged 40-49 years, 1.9% for those aged 50-59 years, and 2.4% for those aged 60-69 years [35]. These rates are 2 to 5 times lower than those observed in our study, indicating that patients with CHD develop frailty earlier in life than non-CHD individuals. A study by Sinclair et al. reported a 8.1% prevalence of frailty in adults aged 50 years or older in England [37]. They observed higher frailty rates in coastal areas, which might explain the elevated frailty numbers in England compared to our international study. Moreover, they used a different frailty assessment and included older patients, contributing to the variation [37].

In our sample, exhaustion was the most prevalent component of the Fried frailty phenotype, occurring in one-quarter of the patients. This may be a typical feature for the aging patient with CHD, as community samples report exhaustion in only 7.5-12% [35,36]. Exhaustion may result from factors like anemia, endothelial function, cyanosis, drug side effects or iron deficiency. The number of unpaired handgrip strength in our patients was, however, in line with that of people in the community (13-14.8%) [35,36]. This was rather surprising, because two studies reported a prevalence of sarcopenia in 16% and 51% of patients with (mild and) complex CHD, although their population was fairly young with a mean age of 37 and 36 years [38,39].

Multivariable analysis showed that the pre-frail phenotype was associated with older age, female sex, simple heart defects, higher physiological stage, more catheter interventions, more comorbidities, and a lower country-level income. Frailty was related to older age, female sex, higher physiological stage, and more comorbidities. These results align with community samples, where age [34,36], female sex [34,36,40], multimorbidity [36], and socio-economic deprivation at individual or country level [36,40] predicted (pre-)frailty.

Studies show frailty is related to reduced bone mineral density and sarcopenia, especially in women due to menopause-related estrogen loss and lower muscle strength [41]. This might accelerate the frailty development in women and may explain the association with sex as found in our study [10].

The disparity in predictor variables of frail and pre-frail may reflect differences in statistical power, because the cohort of frail people is much smaller than that of pre-frail and robust patients. The fact that patients with simple heart lesions were more often pre-frail indicates that people with conditions that are benign from a cardiovascular point of view are still vulnerable to complications from a functional perspective [42]. On the other hand, it is possible that no strong association was found between CHD complexity and frailty due to survival bias. Notably, only 18% of the frailty variance was determined by the factors in our model. Hence, other factors, like nutritional deficiencies, hormonal changes, health behavior and inflammation may influence the frailty phenotype in these patients as well [29].

Cognitive function in patients with CHD

Neurodevelopmental research in CHD has historically been dominated by studies in children, adolescents or young adults [14,43,44]. Research on neurocognition in middle-aged and older people with CHD is rather scarce. However, besides the known neurodevelopmental issues, patients with CHD are prone to a neurocognitive decline because risk factors for cognitive

deterioration, such as heart failure, atrial fibrillation, hypertension, diabetes, and coronary artery disease, are more prevalent [45]. Consequently, cerebral blood flow and brain volumes are affected, leading to a higher prevalence and earlier onset of dementia in people with CHD [45-47]. Early-onset dementia in CHD was substantiated by an incidence rate of 0.03/1000 person-years [46], and a prevalence of 2.9/1000 in middle-aged patients [47]. This exceeds the rates in the general population, in which an incidence rate of 0.01/1000 person-years [46] and a prevalence of 1.2/1000 was found [47].

In the present study, four in ten patients experienced some degree of cognitive dysfunction. This prevalence approximates the 34% that was found in a self-report study in patients aged 30±10 years, with mild to complex CHD [48]. However, a US-based study conducted in adolescents and young adults with CHD using the MoCA found a median score of 23 and a 69% prevalence of cognitive problems [16]. This was significantly worse than the median score of 28 and the prevalence of 13% in healthy controls [16]. The fact that patients in our sample are doing cognitively better could be due to survival bias, may be explained by inter-country variation, or could be the result of methodological differences. Therefore, our findings stress the importance of conducting this kind of research on large samples in an international context.

Cognitive dysfunction in patients with CHD was associated with older age, more comorbidities, and living in a middle-income country. In contrast to previous studies, there was no relationship between cognitive dysfunction and the complexity of the heart disease nor the physiological stage, when adjusted for other patient-related factors [49,50]. Nonetheless, prior research described disease complexity as a risk factor for cognitive impairment in adults with CHD [48,51]. The incongruence with our findings may be due to differences in assessment, and the fact that we adjusted for other patient factors.

Consequences of frailty and cognitive dysfunction

Both frailty and pre-frailty are associated with adverse health outcomes. A meta-analysis demonstrated that pre-frail individuals have an increased risk for faster onset of any type of cardiovascular disease [52]. Further, frail and pre-frail people have a higher mortality risk [36]. In our study, we could not find a higher use of outpatient visits or cardiac admissions in frail or pre-frail patients. However, patients with adequate cognitive function were likely to have more outpatient clinic visits. The most probable reason is that patients with complex heart defects, who by default have higher follow-up rates, had a lower, albeit non-significant proportion of cognitive dysfunction. In addition, patients with complex heart lesions could be likely to be more engaged in their health, and therefore more invested in their care. Another possible explanation could be that impaired cognitive function may lead to reduced healthcare utilization.

Strengths and limitations

This study has several strengths. As part of APPROACH-IS II, the study comprised more than 800 patients from 11 countries around the world. Since the assessment was done during a scheduled outpatient visit, there was a high degree of complete data. We used validated assessments of both frailty and cognitive functioning, namely the Fried frailty phenotype and the MoCA [10,16]. The validity of the MoCA has been specifically tested in adults with CHD [16].

However, there are also some limitations to bear in mind in the interpretation of the findings. First, APPROACH-IS II has used a cross-sectional design. Consequently, no causality in the relationships can be determined. Second, the study is prone to survivorship bias. Since patients with complex CHD, poor physiological status and co-morbidities are less likely to reach older age, they may be underrepresented in our sample. Consequently, the prevalence of cognitive functioning and frailty in congenital heart disease may be underestimated. Third,

APPROACH-IS II is mainly aiming to measure patient-reported outcomes (PROs). Therefore, only patients with the physical or mental capabilities to complete such self-report questionnaires were included. This may have led to an underrepresentation of people with cognitive disabilities, and thus an overestimation of the cognitive function of the CHD population. Fourth, we did not have a control group. Therefore, we cannot directly compare the differences between our individuals with or without CHD. Fifth, we used the original CCI that was based on weights assigned in 1984. Future research should consider using the updated CCI due to advances in chronic disease management and treatments, which caused a decrease in the one-year mortality and assigned weights [32,53]. Sixth, only two upper-middle-income and no low-income countries participated in this study. Since frailty and cognitive dysfunction is associated with country income, the prevalence would be higher if more lower income countries would have been included. Therefore, caution is needed when generalizing these data to a global population of ACHD patients, including patients from lower-income countries. Lastly, we initially aimed to include only patients with moderate and complex CHD [24]. However, deviations from the protocol at certain centers resulted in the inadvertent inclusion of some patients with simple heart defects. This led to the discovery that even patients with mild CHD experienced frailty and cognitive impairment, challenging common beliefs that simple heart defects are benign and do not have substantial consequences. Nonetheless, the number of included patients with simple CHD is limited, which may have reduced the statistical power.

CONCLUSION

Almost half of the sample of patients with CHD were (pre-)frail, and four out of ten displayed some degree of cognitive dysfunction. Frailty was associated with being older, female, having a worse physiological stage and having more comorbidities. Pre-frailty was related to the same predictor variables, plus mild heart defects and lower country-level income. Cognitive

dysfunction was also linked to increased age, more comorbidities and lower country-level income. The fact that frailty and cognitive dysfunction were slightly, but not significantly, more prevalent in mild CHD indicates that these issues can affect all types of heart defects. Pre-frailty and frailty were not associated with a higher healthcare utilization. However, patients with adequate cognitive function had more outpatient clinic visits. The present study offers the first clear clinical profile of middle-aged and older patients with CHD in terms of frailty and cognition, which expresses the functional consequences of aging.

CLINICAL PERSPECTIVES

Competency in Systems-Based Practice: In adults with congenital heart disease (ACHD) frailty and cognitive dysfunction are associated with older age, more severe physiological derangement, and a greater number of comorbidities, and to some extent female sex and lower national income rather than the anatomical complexity of the cardiac condition.

Translational Outlook: Better understanding of the causes and trajectories of frailty and cognitive impairment among patients with ACHD could facilitate development of preventive strategies and improvement in systems of care.

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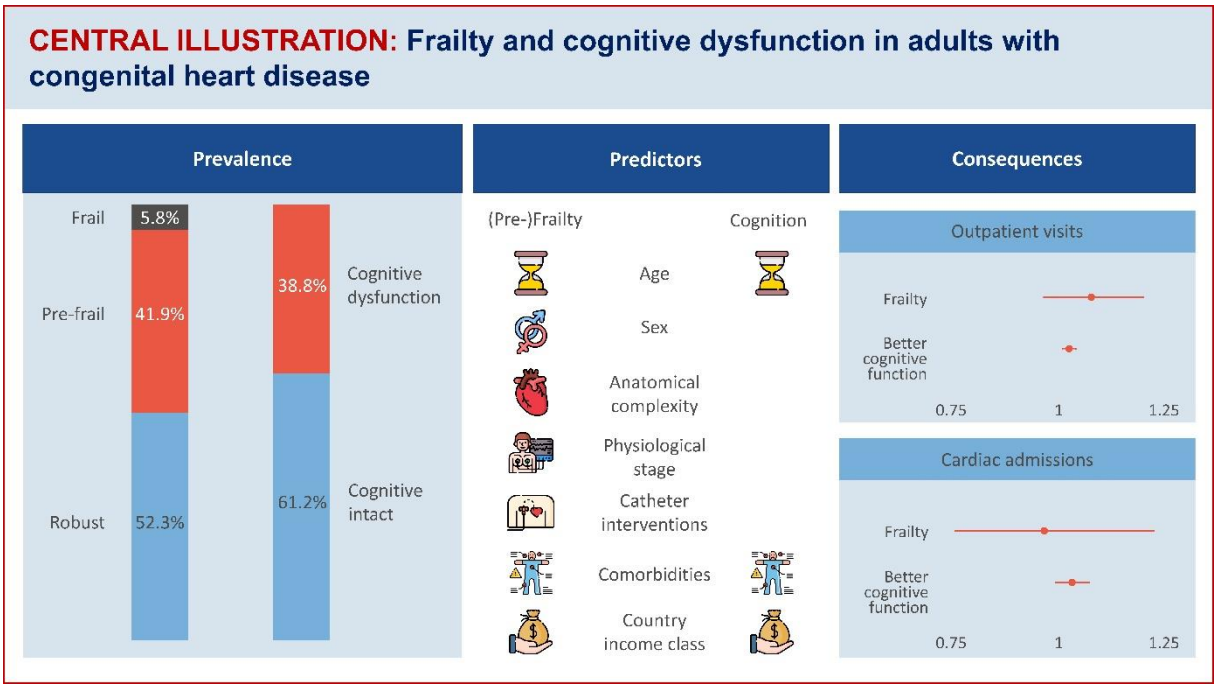
Figure Legend

Central illustration: Frailty and cognitive dysfunction in adults with congenital heart disease.



Legend: Prevalence, predictor variables and consequences of frailty and cognitive dysfunction in older adults with congenital heart disease.

TABLES/FIGURES

Table 1. Demographic and clinical characteristics of the study population (n=814).

Median age (years), (n=812)	52.0 [IQR 45.0-61.0]
Sex (n=812)	
Male	394 (48.5%)
Female	418 (51.5%)
Disease complexity, as per ACHD AP classification (n=810)	
Mild	103 (12.7%)
Moderate	568 (70.1%)
Severe	139 (17.2%)
Physiological stage, as per ACHD AP classification (n=813)	
A	62 (7.6%)
B	188 (23.1%)
C	478 (58.8%)
D	85 (10.5%)
Charlson comorbidity index (n=814)	
No comorbidities	489 (60.1%)
Mild comorbidities	285 (35.0%)
Moderate comorbidities	37 (4.5%)
Severe comorbidities	3 (0.4%)
Number of interventional catheterizations (n=811)	
0	538 (66.3%)
1	184 (22.7%)
2	57 (7.0%)
3	20 (2.5%)
4	9 (1.1%)
6	3 (0.4%)
Number of cardiac surgeries (n=807)	
0	193 (23.9%)
1	287 (35.6%)
2	219 (27.1%)
3	85 (10.5%)
4	16 (2.0%)
5	4 (0.5%)
6	1 (0.1%)
8	2 (0.2%)
History of arrhythmias (n=811)	
No	440 (54.3%)
Yes, not requiring treatment	68 (8.4%)
Yes, stable on treatment	276 (34.0%)
Yes, but refractory arrhythmia (not responding to treatment)	27 (3.3%)
Cyanosis or hypoxemia (n=810)	
No (resting saturation >90%)	768 (94.8%)
Mild/moderate (resting saturation 85-90%)	21 (2.6%)
Severe (resting saturation < 85%)	21 (2.6%)
Ventricular dysfunction (n=806)	

No	473 (58.5%)
.Mild	207 (25.6%)
Moderate/severe	129 (15.9%)
Current organ dysfunction (n=804)	
No, renal, pulmonary and/or kidney function is normal	755 (93.9%)
Yes, evidence of end-organ dysfunction responsive to treatment	36 (4.5%)
Yes, evidence of refractory end-organ dysfunction	13 (1.6%)
Cardiac admissions over past 5 years (n=798)	
No cardiac admissions	420 (52.6%)
1-10 admissions	369 (46.2%)
11-20 admissions	6 (0.8%)
21-30 admissions	2 (0.3%)
> 30 admissions	1 (0.1%)
Cardiac outpatient visits over past 5 years (n=803)	
No cardiac outpatients visits	8 (1.0%)
1-5 visits	407 (50.7%)
6-10 visits	237 (29.5%)
11-20 visits	120 (14.9%)
21-30 visits	16 (2.0%)
> 30 visits	15 (1.9%)
World Bank Income Class	
High-Income country	740 (90.9%)
Upper-Middle-Income country	74 (9.1%)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CCTGA, congenitally corrected transposition of the great arteries; d-TGA, dextro-transposition of the great arteries; HCM, hypertrophic cardiomyopathy; IQR, Interquartile range; l-TGA, levo-transposition of the great arteries; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Table 2: Frailty phenotype and Montréal Cognitive Assessment criteria in adults with congenital heart disease.

Fried frailty phenotype	**n (%)**
Exhaustion	213 (26.5%)
Poor grip strength	124 (15.6%)
Slow walking speed	90 (11.2%)
Low physical activity	86 (10.7%)
Unintentional weight loss	82 (10.1%)
Montréal Cognitive Assessment	**Mean ± SD**
Visuo-spatial/executive function (0-5)	4.14 ± 1.15
Naming of animals (0-3)	2.89 ± 0.38
Attention: List of digits (0-2)	1.78 ± 0.47
Attention: List of letters (0-1)	0.94 ± 0.25
Attention: Calculation exercise (0-3)	2.56 ± 0.84
Language: Repeat sentence (0-2)	1.79 ± 0.48
Language: Words starting with same letter (0-1)	0.73 ± 0.44
Abstraction (0-2)	1.69 ± 0.58
Delayed recall of words (0-5)	3.05 ± 1.55
Orientation (0-6)	5.92 ± 0.40

SD=Standard Deviation

Table 3: Frailty and cognition in adults with congenital heart disease.

	Frailty (n=811)			Cognition (n=783)	
	Robust	Pre-frail	Frail	Cognitive intact	Cognitive dysfunction
Total sample	424 (52.3%)	340 (41.9%)	47 (5.8%)	479 (61.2%)	304 (38.8%)
Age class					
40-49 y	194 (58.3%)	128 (38.4%)	11 (3.3%)	221 (66.6%)	111 (33.4%)
50-59y	131 (53.5%)	102 (41.6%)	12 (4.9%)	159 (66.5%)	80 (33.5%)
≥ 60y	98 (42.4%)	109 (47.2%)	24 (10.4%)	99 (46.7%)	113 (53.3%)
Sex					
Men	234 (59.5%)	146 (37.2%)	13 (3.3%)	240 (62.8%)	142 (37.2%)
Women	189 (45.4%)	193 (46.4%)	34 (8.2%)	239 (59.6%)	162 (40.4%)
Anatomical complexity					
Mild CHD	42 (40.8%)	54 (52.4%)	7 (6.8%)	61 (61.0%)	39 (39.0%)
Moderate CHD	308 (54.4%)	226 (39.9%)	32 (5.7%)	328 (59.6%)	222 (40.4%)
Complex CHD	72 (52.2%)	58 (42.0%)	8 (5.8%)	89 (67.9%)	42 (32.1%)
Physiological stage					
Stage A	40 (64.5%)	21 (33.9%)	1 (1.6%)	36 (58.1%)	26 (41.9%)
Stage B	115 (61.5%)	69 (36.9%)	3 (1.6%)	126 (67.7%)	60 (32.3%)
Stage C	244 (51.2%)	204 (42.8%)	29 (6.1%)	277 (60.5%)	181 (39.5%)
Stage D	25 (29.8%)	45 (53.6%)	14 (16.7%)	41 (52.6%)	37 (47.4%)
Comorbidities					
No comorbidities	291 (59.5%)	176 (36.0%)	22 (4.5%)	298 (63.3%)	173 (36.7%)
Mild comorbidities	131 (46.3%)	133 (47.0%)	19 (6.7%)	168 (60.9%)	108 (39.1%)
Moderate comorbidities	2 (5.6%)	30 (83.3%)	4 (11.1%)	15 (42.9%)	20 (57.1%)
Severe comorbidities	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	3 (100.0%)
World Bank Income Class					
High-Income country	396 (53.7%)	301 (40.8%)	40 (5.4%)	450 (63.3%)	261 (36.7%)
Upper-Middle-Income country	28 (37.8%)	39 (52.7%)	7 (9.5%)	31 (41.9%)	43 (58.1%)

Table 4. Predictor variables of frailty and cognitive function in patients with congenital heart disease.

	Frailty		**Cognitive function**
	Pre-frail vs Robust OR (95% CI)	Frail vs Robust OR (95% CI)	Cognitive dysfunction vs normal cognition OR (95% CI)
Age	**1.02 (1.00-1.04)***	**1.06 (1.03-1.10)*****	**1.03 (1.02-1.05)*****
Sex			
Men	**0.64 (0.47-0.87)****	**0.31 (0.15-0.63)****	0.97 (0.71-1.31)
Women	*Reference*	*Reference*	*Reference*
Anatomical complexity			
Mild	**1.98 (1.07-3.68)***	2.00 (0.56-7.11)	1.06 (0.57-1.97)
Moderate	0.92 (0.59-1.41)	0.92 (0.37-2.27)	1.20 (0.77-1.86)
Complex	*Reference*	*Reference*	*Reference*
Physiological stage (AP classification)			
A	**0.26 (0.12-0.59)****	**0.05 (0.01-0.42)****	0.96 (0.46-2.01)
B	**0.36 (0.20-0.67)****	**0.05 (0.01-0.21)*****	0.56 (0.33-1.05)
C	**0.51 (0.29-0.90)***	**0.23 (0.10-0.53)****	0.77 (0.46-1.30)
D	*Reference*	*Reference*	*Reference*
Number of catheter interventions	**1.26 (1.06-1.50)****	1.32 (0.92-1.92)	1.00 (0.84-1.19)
Number of cardiac surgeries	1.02 (0.87-1.19)	1.09 (0.81-1.47)	0.95 (0.82-1.11)
Comorbidity Index (continuous)	**1.36 (1.17-1.59)*****	**1.40 (1.13-1.75)*****	**1.16 (1.02-1.32)***
World Bank Income Class			
High-Income country	**0.50 (0.28-0.86)***	0.37 (0.13-1.03)	**0.48 (0.28-0.80)****
Upper-Middle-Income country	*Reference*	*Reference*	*Reference*

*p<0.05; **p<0.01; ***p<0.001; 95% CI=95% confidence interval; OR=odds ratio.