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

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Keywords:

aging; cognition; congenital heart defects; frailty; frailty phenotype.

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ABBREVIATIONS AND ACRONYMS

ACHD AP = adult congenital heart disease anatomic and physiologic

CHD = congenital heart disease
CCI = Charlson Comorbidity Index
GNI = gross national income
MoCA = Montreal Cognitive Assessment

Abstract

Background:

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

Objectives:

The authors 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 Montreal Cognitive Assessment.

Results:

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

Conclusions:

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

Congenital heart disease (CHD) is the most prevalent birth defect worldwide, occurring in almost 1 in 100 newborns.¹ Although the life expectancy for these patients was limited 5 decades ago, now 90% of children with CHD reach adulthood because of 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, health care use, and mortality rates.^{5,6} Understanding their evolving medical and psychosocial challenges is vital for mapping their specific health care needs and maintaining longevity and quality of life.^{6,7} However, 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 physiologic capacity across multiple organ systems may be approximated to frailty. Frailty is defined as a decline in the 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, prefrail, or frail based on 5 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, and preoperative and postoperative risks. Medical and surgical therapies and resulting hypoperfusion also contribute to the development of neurologic 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 because impairment may adversely affect their quality of life, health care needs, and mortality.^{15,22}

It is important to consider whether frailty and cognitive impairment are affected by socioeconomic 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 to do the following: 1) assess frailty and cognitive impairment in an international sample of middle-

aged and older adults with CHD; 2) evaluate whether patient-related factors and country income level are predictor variables for frailty and cognition; and 3) to explore consequences in terms of hospital admissions and outpatient visits.

METHODS

STUDY DESIGN.

This study was part of APPROACH-IS II (Assessment of Patterns of Patient-Reported Outcomes in Adults With Congenital Heart Disease– International Study 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 substudy focusing on frailty and cognitive impairment, patients were enrolled from 17 centers in 11 countries categorized as having 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: 1) diagnosed with CHD; 2) aged 40 years or older at study entry; 3) diagnosed with CHD before the age of 10 years; 4) receiving care at an adult CHD center; and 5) 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: 1) 40 to 50 years; 2) 51 to 60 years; and 3) older than 60 years.

STUDY PROCEDURE.

Data were collected from August 1, 2019, until November 31, 2022. The original data collection period was extended because of pauses during the acute waves of the COVID-19 pandemic. Participants received unique study numbers, and their data were encoded in the Research Electronic Data Capture (REDCap) data management platform (Vanderbilt University).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](https://clinicaltrials.gov/ct2/show/study/NCT04902768)).

VARIABLES AND INSTRUMENTS.

Demographic data were collected through self-report questionnaires completed by patients, and medical data (eg, CHD diagnosis, number of catheter interventions, number of cardiac surgeries, hospital admissions for cardiac reasons of at least 1 day over the past 5 years, and cardiac outpatient clinic visits over the past 5 years) were abstracted from medical records. Moreover, the adult congenital heart disease anatomic and physiologic (ACHD AP) classification, incorporating both anatomic and physiologic factors, was recorded.²⁸ The incorporated physiologic 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, prefrail, or frail based on 5 criteria: self-reported unintentional weight loss, exhaustion, and physical activity; assessment of muscle weakness using a handgrip dynamometer (stratified by sex and body mass index); and the performance of a 4.5-m walking speed test (stratified by sex and height).¹⁰ Participants were considered frail if they met 3 or more of the 5 criteria, prefrail 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 Montreal Cognitive Assessment (MoCA), which evaluates multiple cognitive domains, including visuospatial 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 4 categories: no comorbidities (score of 0), mild comorbidities (score of 1-3), moderate comorbidities (score of 4-7), 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 of \$13,846 USD), upper middle income (GNI of \$4,466-\$13,845 USD), lower middle income (GNI of \$1,136-\$4,465 USD), and low income (GNI of \$1,135 USD).³³

TABLE 1 Demographic and Clinical Characteristics of the Study Population (N = 814)	
Age, y (N = 812)	52.0 (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)
No. 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)
No. 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)

Continued on the next page

TABLE 1 Continued	
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 y (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 y (N = 803)	
No cardiac outpatient 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)
Values are n, median (Q1-Q3), or n (%).	
ACHD AP – Adult Congenital Heart Disease Anatomic and Physiological.	

STATISTICAL ANALYSIS.

Data analysis was performed using IBM SPSS Statistics, version 29 (IBM Corp). Normality and homogeneity were checked using the Shapiro-Wilk and Levene tests. Data are presented as mean +/- SD, median (Q1-Q3), absolute number (%), or OR (95% CI). The Spearman rho test was used for correlation analysis. The relationships between frailty and sex, age, CHD complexity, physiologic stage (ie, 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 physiologic component of the ACHD AP classification. The null hypothesis was rejected for P values of <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 to 50 years (43.7%), 239 were aged 51 to 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 5 years, most patients (50.7%) had 1 to 5 cardiac outpatient visits (mean: 7.8 +/- 8.1). Additionally, almost one-half of the sample (47.4%) had at least 1 cardiac admission the past 5 years (mean: 1.3 +/- 3.9). The demographic and clinical characteristics of the sample are presented in [Table 1](#). The frequency distribution of heart defects is described in [Supplemental Table 1](#).

FRAILITY AND COGNITIVE FUNCTIONING.

Exhaustion was the most prevalent frailty criterion, 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 prefrail, and 5.8% were frail ([Table 3](#)). The prevalence of frailty was 3.3% in patients aged 40 to 49 years, 4.9% in patients aged 50 to 59 years, and 10.4% in those aged 60 years 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 physiologic stage, patients in stage C or D were frail in 6.1% and 16.7% of the cases, respectively, 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 2 upper middle-income countries were prefrail in 52.7% of the cases and frail in 9.5%, whereas these values were 40.8% and 5.4% in high-income countries, respectively ([Table 3](#)).

The median MoCA score was 27 (Q1-Q3: 24-29). The score distribution is given in [Supplemental Figure 1](#). The different MoCA item scores can be found in [Table 2](#). Based on the established cutoff of 26, 38.8% of the patients displayed cognitive dysfunction ([Table 3](#)). Among patients aged 60 years 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 physiologic stage D and in those with more comorbidities ([Table 3](#)). A weak negative correlation was found between being frail and cognitive function ($r = -0.210$; $P < 0.001$). The frequency distribution of frailty vs cognitive function is provided in [Supplemental Table 2](#), demonstrating a certain, albeit limited, coexistence of frailty and cognitive dysfunction.

PREDICTOR VARIABLES OF FRAILITY AND COGNITIVE DYSFUNCTION.

Multivariable multinomial regression analysis showed that older age, female sex, higher physiologic stage, and more comorbidities were associated with a higher likelihood of having a prefrail 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 prefrail 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](#)).

TABLE 2 Frailty Phenotype and Montreal Cognitive Assessment Criteria in Adults With Congenital Heart Disease

Fried frailty phenotype	
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)
Montreal Cognitive Assessment	
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

Values are n (%) or mean ± SD.

CONSEQUENCES OF FRAILTY AND COGNITIVE DYSFUNCTION.

The number of outpatient visits in the preceding 5 years was 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 physiologic 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 5 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.

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 health care usage. An overview of the findings can be found in the [Central Illustration](#).

FRAILTY IN PATIENTS WITH CHD.

Almost one-half of the patients enrolled in this study were classified as prefrail 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, whereas 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 al³⁵ found frailty rates of 1.4% for people aged 40 to 49 years, 1.9% for those aged 50 to 59 years, and 2.4% for those aged 60 to 69 years. 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 al³⁷ reported an 8.1% prevalence of frailty in adults aged 50 years or older in England. 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

TABLE 3 Frailty and Cognition in Adults With Congenital Heart Disease

	Frailty (n = 811)			Cognition (n = 783)	
	Robust	Prefrail	Frail	Cognitive Intact	Cognitive Dysfunction
Total sample	424 (52.3)	340 (41.9)	47 (5.8)	479 (61.2)	304 (38.8)
Age class, y					
40-49	194 (58.3)	128 (38.4)	11 (3.3)	221 (66.6)	111 (33.4)
50-59	131 (53.5)	102 (41.6)	12 (4.9)	159 (66.5)	80 (33.5)
≥60	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					
A	40 (64.5)	21 (33.9)	1 (1.6)	36 (58.1)	26 (41.9)
B	115 (61.5)	69 (36.9)	3 (1.6)	126 (67.7)	60 (32.3)
C	244 (51.2)	204 (42.8)	29 (6.1)	277 (60.5)	181 (39.5)
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)

Values are n (%).
CHD = congenital heart disease.

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, because community samples report exhaustion in only 7.5% to 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 2 studies reported a prevalence of sarcopenia in 16% and 51% of patients with (mild and) complex CHD, although their populations were fairly young, with mean ages of 37 and 36 years.^{38,39}

Multivariable analysis showed that the prefrail phenotype was associated with older age, female sex, simple heart defects, higher physiologic stage, more catheter interventions, more comorbidities, and a lower country-level income. Frailty was related to older age, female sex, higher physiologic stage, and more comorbidities. These results align with community

samples, where age,^{34,36} female sex,^{34,36,40} multimorbidity,³⁶ and socioeconomic deprivation at the individual or country level^{36,40} predicted (pre-) frailty.

TABLE 4 Predictor Variables of Frailty and Cognitive Function in Patients With Congenital Heart Disease

	Frailty		Cognitive Function
	Prefrail vs Robust	Frail vs Robust	Cognitive Dysfunction vs Normal Cognition
Age	1.02 (1.00-1.04) ^a	1.06 (1.03-1.10) ^b	1.03 (1.02-1.05) ^b
Sex			
Men	0.64 (0.47-0.87) ^c	0.31 (0.15-0.63) ^c	0.97 (0.71-1.31)
Women	Reference	Reference	Reference
Anatomical complexity			
Mild	1.98 (1.07-3.68) ^a	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) ^c	0.05 (0.01-0.42) ^c	0.96 (0.46-2.01)
B	0.36 (0.20-0.67) ^c	0.05 (0.01-0.21) ^b	0.56 (0.33-1.05)
C	0.51 (0.29-0.90) ^a	0.23 (0.10-0.53) ^c	0.77 (0.46-1.30)
D	Reference	Reference	Reference
No. of catheter interventions	1.26 (1.06-1.50) ^c	1.32 (0.92-1.92)	1.00 (0.84-1.19)
No. 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) ^b	1.40 (1.13-1.75) ^b	1.16 (1.02-1.32) ^a
World Bank income class			
High-income country	0.50 (0.28-0.86) ^a	0.37 (0.13-1.03)	0.48 (0.28-0.80) ^c
Upper-middle- income country	Reference	Reference	Reference

Values are OR (95% CI). ^aP < 0.05. ^bP < 0.001. ^cP < 0.01.

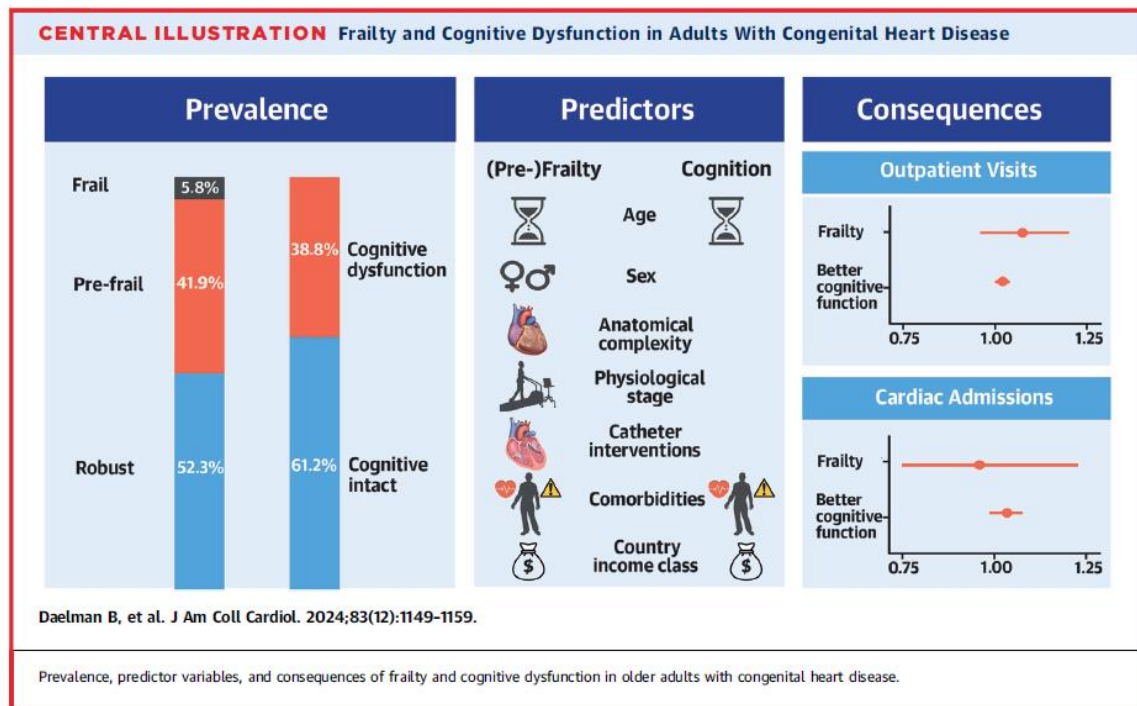
Studies show that frailty is related to reduced bone mineral density and sarcopenia, especially in women because of menopause-related estrogen loss and lower muscle strength.⁴¹ This might accelerate the frailty development in women and may explain the association with sex as found in our study.¹⁰

The disparity in predictor variables of frail and prefrail may reflect differences in statistical power, because the cohort of frail people is much smaller than that of prefrail and robust patients. The fact that patients with simple heart lesions were more often prefrail 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 because of 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 per 1,000 person-years⁴⁶ and a prevalence of 2.9 per 1,000 in middle-aged patients.⁴⁷ This exceeds the rates in the general population, in which an incidence rate of 0.01 per 1,000 person-years⁴⁶ and a prevalence of 1.2 per 1,000 was found.⁴⁷



In the present study, 4 in 10 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 U.S.-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 control individuals.¹⁶ The fact that patients in our sample are doing cognitively better could be because of survival bias, may be explained by intercountry variation, or could be the result of methodologic 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 physiologic 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 caused by differences in assessment and the fact that we adjusted for other patient factors.

CONSEQUENCES OF FRAILITY AND COGNITIVE DYSFUNCTION.

Both frailty and prefrailty are associated with adverse health outcomes. A meta-analysis demonstrated that prefrail individuals have an increased risk for faster onset of any type of cardiovascular disease.⁵² Further, frail and prefrail 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 prefrail 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 nonsignificant—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 health care use.

STUDY STRENGTHS AND LIMITATIONS.

This study has several strengths. As part of APPROACH-IS II, the study comprised >800 patients from 11 countries around the world. Because 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 used a cross-sectional design. Consequently, no causality in the relationships can be determined. Second, the study is prone to survivorship bias. Because patients with complex CHD, poor physiologic status, and comorbidities 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. 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, which is based on weights assigned in 1984. Future research should consider using the updated CCI because of advances in chronic disease management and treatments, which caused a decrease in the 1-year mortality and assigned weights.^{32,53} Sixth, only 2 upper-middle-income and no low-income countries participated in this study. Because frailty and cognitive dysfunction are associated with country income, the prevalence would be higher if more lower-income countries had been included. Therefore, caution is needed when generalizing these data to a global population of ACHD patients, including patients from lower-income countries. Finally, 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.

CONCLUSIONS

Almost one-half of the sample of patients with CHD were (pre-) frail, and 4 of 10 displayed some degree of cognitive dysfunction. Frailty was associated with being older, being female, having a worse physiologic stage, and having more comorbidity. Prefrailty 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. Prefrailty and frailty were not associated with a higher health care use. 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.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: In adults with CHD, frailty and cognitive dysfunction are associated with older age; more severe physiologic derangement; a greater number of comorbidities; and, to some extent, female sex and lower national income rather than the anatomic complexity of the cardiac condition.

TRANSLATIONAL OUTLOOK: Better understanding of the causes and trajectories of frailty and cognitive impairment among adults with CHD could facilitate the development of preventive strategies and improvement in systems of care.

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