ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 47–54
Published online 18 December 2019 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12542

ORIGINAL RESEARCH ARTICLE

Cognitive impairment in patients with heart failure: an international study

Ercole Vellone[1], Oronzo Chialà[1], Josiane Boyne[2], Leonie Klompstra[3], Lorraine S. Evangelista[4], Maria Back[5], Tuvia Ben Gal[6,7], Jan Mårtensson[8], Anna Strömberg[5] and Tiny Jaarsma[3]*

[1]*Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy;* [2]*Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands;* [3]*Department of Social and Welfare Studies, Faculty of Health Science, Linköping University, Linköping, Sweden;* [4]*Sue & Bill Gross School of Nursing, University of California Irvine, Irvine, CA, USA;* [5]*Division of Physiotherapy, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden;* [6]*Department of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel;* [7]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel;* [8]*Department of Nursing, School of Health and Welfare, Jönköping University, Jönköping, Sweden*

Abstract

Aims Cognitive impairment (CI) in heart failure (HF) patients has mostly been studied in single countries in specific health care settings. Sociodemographic and clinical predictors of the global CI and CI dimensions are still unclear. We described CI in a diverse HF population recruited in several countries and in different health care settings and investigated sociodemographic and clinical factors associated with the global and specific CI dimensions in HF patients.

Methods and results A secondary analysis from the baseline data of the Wii-HF trial. Patients (n = 605) were enrolled in Sweden, Italy, Israel, The Netherlands, Germany, and the United States. We used the Montreal Cognitive Assessment to evaluate CI and the 6 minute walk test (6MWT) to measure exercise capacity. Patients were on average 67 years old (SD, 12), and 86% were in New York Heart Association Class II and III. The mean Montreal Cognitive Assessment score was 24 (SD, 4), and 67% of patients had at least a mild CI. The item evaluating short-term memory had a considerable proportion of low scoring patients (28.1%). Worse CI was associated with patients' older age, lower education, and lower 6MWT scores (R^2 = 0.27). CI dimension scores were differently associated with specific clinical and demographic variables, but the 6MWT scores were associated with five out of seven CI dimension scores.

Conclusions CI is an important problem in HF patients, with specific challenges in regard to memory. Exercise capacity is a modifiable factor that could be improved in HF patients with the potential to improve cognition and other outcomes in this population.

Keywords Heart failure; Cognitive impairment; Exercise capacity

Received: 9 July 2019; Revised: 14 September 2019; Accepted: 23 September 2019
**Correspondence to: Tiny Jaarsma, Department of Medical and Health Sciences, Linkoping University, Linkoping, Sweden. Email: tiny.jaarsma@liu.se*

Introduction

Heart failure (HF) is a prominent public health problem in the western world as a result of its rising prevalence and incidence.[1] Because of the ageing population and the improved treatment of cardiac diseases, there are about 15 million people affected by HF in Europe[1] and more than 6 million in the United States.[2] HF is associated with several symptoms (e.g. shortness of breath and fatigue) that impair quality of life[3] and is also associated with high mortality rates, recurrent hospitalizations, and high direct and indirect costs.[4–6]

Cognitive impairment (CI) is a common co-morbid condition in patients with HF.[7] Several studies have shown that CI in HF ranges between 20% and 80%,[7,8] and that CI is associated with poor HF outcomes, such as death, hospital readmission, and poor self-care.[9] Despite that, the pathophysiology of CI in patients with HF remains unclear,[10] although several studies have succeeded in identifying its sociodemographic and clinical predictors. Sociodemographic predictors of CI in HF include older age,[11] female gender, and lower education;[12] and clinical predictors include decreased physical activity,[13] co-morbidities[14] and HF severity [i.e. higher New York Heart Association (NYHA) Class and lower ejection fraction].[15]

Although several studies have addressed CI in patients with HF,[7,8] the existing studies have mostly been conducted in small samples, in single countries, and specific health care settings[8] (e.g. only rehabilitation or outpatient settings). Also, the existing studies report inconsistencies among sociodemographic and clinical predictors of CI (i.e. gender, age, education, time after diagnosis, NYHA class, ejection fraction, comorbidities, and exercise capacity) and have not identified the sociodemographic and clinical predictors of specific cognitive dimensions in patients with HF (e.g. memory). Since patients with HF receive care in a large diversity of health care settings and their cognitive dimensions might be affected by different sociodemographic and clinical variables, we conducted this study to (i) describe CI in a diverse HF population recruited in several countries and in different health care settings and (ii) investigate sociodemographic and clinical factors (i.e. gender, age, education, time after diagnosis, NYHA class, ejection fraction, comorbidities, and exercise capacity) associated with global and specific CI in patients with HF.

Methods

Design

This study is a secondary analysis from the baseline data of the Wii-HF study,[16] a randomized controlled trial (ClinicalTrial.gov identifier: NCT01785121) aimed at evaluating the effect of exergaming on improving exercise capacity in patients with HF enrolled in six countries.

Sample and settings

In the Wii-HF study, patients with HF were enrolled in different settings in Sweden, Italy, Israel, The Netherlands, Germany, and the United States. In Sweden, patients were enrolled in outpatient clinics of five hospitals, two university hospitals, two county hospitals, and one community hospital. In Italy, all patients were enrolled in a rehabilitation hospital; in Israel, patients were recruited from an advanced HF treatment centre; in The Netherlands and the United States, patients were enrolled in an outpatient clinic of a university hospital; and in Germany, from a private cardiology practice. Inclusion criteria in each country were (i) diagnosis of HF with reduced or preserved ejection fraction according to the European Society of Cardiology guidelines[1] in NYHA functional Class I-IV; (ii) age older than 18 years; and (iii) able to speak and understand the language of the enrolled country. The exclusion criteria were (i) unable to use the Wii computer because of visual, hearing, and motor impairment; (ii) unable to complete the research instruments; and, (iii) life expectancy shorter than 6 months. CI was not an exclusion criterion; however, if patients were not able to participate because of severe CI (e.g. dementia) as estimated by the study team, the patient was not eligible for the study. Two patients were excluded from the study because of their CI.

Data collection

Several instruments were used in the parent study,[16] but for this analysis we used the instruments described next. The Montreal cognitive assessment (MoCA),[17] is a 30-item valid and reliable instrument that is used worldwide (also in patients with HF) to measure cognition. It evaluates seven cognitive domains as follows: visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation. From the MoCA it is possible to obtain a total score (ranging between 0 and 30) and a dimension score with a different range across the dimensions: a lower score means worse CI both for the total and dimension scores. As defined in prior studies,[18] the following categories of CI can be identified according to the MoCA score: a score between 27 and 30 means 'no to light CI'; a score between 18 and 26 means 'mild CI', a score between 10 and 17 means 'moderate CI', and a score lower than 10 means 'severe CI'.

The Charlson comorbidity index (CCI)[19] is a widely used instrument that evaluates the presence of 19 co-morbid conditions according to their gravity. Each condition could have a possible score from 1 to 6, with a higher score meaning worse co-morbidity.

The 6 minute walk test (6MWT)[20] is a valid, reliable, and objective test of submaximal exercise capacity that measures the distance an individual is able to walk over a total of 6 min on a hard, flat surface. The 6MWT score is obtained from the metres the patient walks in 6 min, with a higher score meaning better exercise capacity. A 6MWT score $>$300 is associated with lower event-free survival at 36 months.[21]

Sociodemographic variables were collected for this study through self-report, including gender, age, education, and marital status. Clinical variables, including time since diagnosis (in months), NYHA functional class and ejection fraction were abstracted from patients' medical records.

Ethical considerations

The protocol of the study was approved by the competent Institutional Review Board in each centre of the six countries in which the patients were enrolled (Sweden DNR 2012/247-31, The Netherlands NL48647.068.14/METC141085; Italy 0052838/272/U.V.F/1, 2014; Israel 0022-13-RMC; Germany S22(a)/2015; United States UCI IRB HS# 2016-2955). Before data collection, patients were fully informed about the study

DOI: 10.1002/ehf2.12542

protocol. Data collection began only after patients signed the informed consent form.

Statistical analysis

Descriptive statistics, including means, standard deviations, and frequencies were used to analyse sociodemographic and clinical variables as well as MoCA, CCI, and 6MWT scores. Comparison across MoCA score categories (no to light CI, mild CI, moderate CI, and severe CI), and patient sociodemographic and clinical variables were performed with χ^2 and ANOVA as appropriate. Spearman's correlations were used to identify the significant correlations among the variables of interest. Variables significantly and independently associated with the total MoCA and dimension scores were identified with a series of regression analyses (enter procedure). In each regression, the independent variables were gender, age, education, time after diagnosis in months, NYHA class, ejection fraction, CCI, and 6MWT scores. Data were analysed with the statistical software IBM SPSS 21.

Results

The total sample included 605 patients with HF (*Table 1*). The sample mean age was 67 (SD, 12), and most were male (71%). In 68% of cases, patients were educated to primary or high school level, and 72% were married. The average CCI score was 2.51 (SD, 1.71), meaning that on average patients suffered from one to two diseases other than HF. The most prevalent comorbidity was diabetes (27%). Eighty-six percent of participants were in NYHA Class II and III, and the mean ejection fraction was 38.7% (11.9). The aetiology of HF was ischemic in 42% of patients. The 84% of patients were treated with angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors, 87% with B-Blocker, 48% with

Table 1 Sociodemographic and clinical characteristics of enrolled patients (n = 605)

	N (%)						
Characteristic	Total sample (n = 605)	Sweden (n = 333)	Italy (n = 96)	Israel (n = 60)	The Netherlands (n = 84)	Germany (n = 24)	United States (n = 8)
Age (mean, SD)	66.9 (11.7)	67.2 (11.8)	71.4 (9.7)	60.5 (12.9)	65.4 (10.6)	69.1 (9.1)	58.1 (8.8)
Gender (male)	430 (71.1)	229 (68.8)	70 (72.9)	44 (73.3)	64 (76.2)	17 (70.8)	6 (75.0)
Education							
Primary School	145 (24.2)	85 (25.9)	36 (37.5)	6 (10.0)	8 (9.5)	10 (21.7)	0 (0)
High School	266 (44.4)	140 (42.7)	36 (37.5)	32 (53.3)	50 (59.5)	6 (25.0)	2 (28.6)
University	177 (29.3)	100 (30.5)	23 (24.0)	21 (35.0)	25 (29.8)	3 (12.5)	5 (71.4)
Other	11 (1.8)	3 (0.9)	1 (1.0)	1 (1.7)	1 (1.2)	5 (20.8)	0 (0)
Marital status							
Married/relationship	430 (71.7)	234 (71.1)	56 (58.3)	50 (83.3)	64 (76.2)	21 (87.5)	5 (71.4)
Single/divorced/widowed	164 (27.3)	93 (28.3)	37 (38.5)	10 (16.7)	20 (23.8)	2 (8.3)	2 (28.6)
Other	6 (1.0)	2 (0.6)	3 (3.1)	0 (0)	0 (0)	1 (4.2)	0 (0)
Charlson Comorbidity	2.51 (1.71)	2.22 (1.40)	2.91 (1.85)	3.61 (2.57)	2.24 (1.18)	3.08 (2.50)	2.50 (1.77)
Index Score (mean, SD)							
Diabetes	159 (26.6)	71 (21.8)	34 (35.4)	23 (38.3)	19 (22.6)	10 (41.7)	2 (25.0)
COPD	108 (18.2)	24 (7.4)	43 (44.8)	21 (35.0)	17 (20.5)	1 (4.2)	2 (25.0)
Stroke	58 (9.7)	32 (9.9)	13 (13.5)	8 (13.3)	5 (6.0)	0 (0)	0 (0)
NYHA class							
I	54 (8.9)	28 (8.8)	4 (4.2)	4 (6.7)	15 (21.1)	1 (4.2)	2 (25.0)
II	350 (57.9)	202 (63.1)	48 (50.0)	33 55.0)	45 (63.4)	17 (70.8)	5 (62.5)
III	171 (28.3)	90 (28.1)	41 (42.7)	23 (38.3)	10 (14.1)	6 (25.0)	1 (12.5)
IV	4 (0.7)	0 (0)	3 (3.1)	0 (0)	1 (1.4)	0 (0)	0 (0)
EF (mean, SD)	38.7 (11.9)	63.4 (10.9)	43.53 (9.8)	32.52 (10.5)	41.68 (13.0)	45.54 (14.9)	39.21 (15.9)
HF aetiology							
Ischemic	249 (42.1)	127 (39.6)	19 (19.8)	32 (53.3)	61 (73.5)	9 (37.5)	1 (14.3)
Non-ischemic	342 (57.9)	194 (60.4)	77 (80.2)	28 (46.7)	22 (26.5)	15 (62.5)	6 (85.7)
Medications							
ACE inhibitor/ARB/ARNI	506 (83.6)	317 (95.5)	40 (41.7)	53 (88.3)	72 (85.7)	20 (83.3)	4 (50.0)
B-Blocker	522 (86.9)	312 (94.3)	52 (54.2)	54 (91.5)	77 (91.7)	21 (87.5)	6 (85.7)
MRA	290 (47.9)	164 (49.5)	26 (27.1)	43 (74.1)	47 (56.0)	8 (33.3)	2 (28.6)
Digoxin	61 (10.1)	26 (7.8)	5 (5.2)	15 (25.9)	10 (11.9)	5 (20.8)	0 (0)
Diuretics	392 (64.8)	195 (55.7)	81 (84.4)	38 (63.3)	58 (69.0)	19 (82.6)	4 (50)
6MWT score (mean, SD)	402.9 (141.7)	449.6 (110.3)	222.4 (114.3)	442.2 (114.6)	432.9 (125.9)	280.5 (116.4)	423.2 (57.5)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist; 6MWT, 6 minute walking test.

mineralocorticoid receptor antagonist, 10% with digoxin, and 65% with digoxin.

The mean total MoCA score was 24.53; 33% of the sample had no or a light CI; 62 % had mild CI; 5% had moderate CI; and 0.3% had severe CI (*Table 2*). *Table 3* reports the number (and percentage) of patients per each MoCA item score. Item 9, evaluating delayed recall, had a considerable proportion of patients (28.1%) who had a low score. The supporting information table reports the mean, SD, minimum, and maximum score per each MoCA item.

Table 4 reports the differences among the variables in relation to the MoCA score categories as follows: no to light CI, mild CI, moderate CI, and severe CI. Patients in the moderate CI and severe CI were significantly older, with less education, with higher CCI scores, in a more advanced NYHA classification and with a lower score at the 6MWT.

Correlation and regression analysis

In the correlation analysis, lower MoCA total scores (meaning worse CI) were significantly associated with older age, lower education, higher NYHA class, lower CCI scores, and lower 6MWT scores (*Table 5*). When all the above variables were entered in a regression model (*Table 6*), lower total MoCA scores (worse CI) were independently associated with patients' older age, lower education, and lower 6MWT scores; the same variables were significantly and independently associated with lower visuospatial/executive dimension scores. Lower naming dimension scores were associated with longer time from HF diagnosis and worse 6MWT scores; lower attention dimension scores were associated with lower education and worse 6MWT scores; lower language dimension scores were associated with lower education and 6MWT scores; lower abstraction dimension scores were associated with lower ejection fraction but with a *P* level of 0.052; lower delayed recall dimension scores were associated only with older age; finally, lower orientation dimension scores were associated with lower 6MWT scores.

Discussion

To our knowledge, this is the first international study to describe CI in a large diverse HF population recruited in six countries and in different health care settings and the first study to identify sociodemographic and clinical variables (i.e. gender, age, education, time after diagnosis, NYHA class, ejection fraction, comorbidities, and exercise capacity) independently associated with specific cognitive dimensions. These two aspects are important because prior studies have described CI in patients with HF but mostly in single countries (e.g. United States)[7] or in single settings (e.g. outpatient settings).[22] HF is a common health problem across the globe,

Table 2 Cognitive impairment in the sample (n = 605)

Moca	Mean (SD) or *N* (%): Total sample (n = 605)	Sweden (n = 333)	Italy (n = 96)	Israel (n = 60)	The Netherland (n = 84)	Germany (n = 24)	USA (n = 8)
MoCA total score	24.35 (3.84)	25.02 (2.95)	20.53 (4.98)	24.45 (3.18)	25.73 (3.05)	25.61 (2.87)	24.13 (6.64)
MoCA categories							
No to Light CI (27–30)	195 (32.7)	119 (36.1)	7 (7.3)	16 (27.6)	38 (46.3)	11 (47.8)	4 (50.0)
Mild CI (18–26)	371 (62.1)	204 (61.8)	68 (70.8)	42 (72.4)	42 (51.2)	12 (52.2)	3 (37.5)
Moderate CI (10–17)	29 (4.9)	7 (2.1)	19 (19.8)	0 (0)	2 (2.4)	0 (0)	1 (12.5)
Severe CI (0–9)	2 (0.3)	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)
MoCA items							
Item n.1 Visuospatial/executive (potential score: 0–5)	3.75 (1.23)	3.83 (1.12)	2.75 (1.38)	3.92 (1.02)	4.33 (0.93)	4.38 (1.10)	3.75 (1.75)
Item n.2 Naming (potential score: 0–3)	2.91 (0.36)	2.97 (0.19)	2.75 (0.65)	2.86 (0.35)	2.87 (0.43)	3.00 (0.00)	2.87 (0.35)
Item n.3 Attention (potential score: 0–2)	1.75 (0.53)	1.78 (0.48)	1.48 (0.74)	1.85 (0.36)	1.82 (0.44)	1.79 (0.41)	1.88 (0.35)
Item n.4 Attention (potential score: 0–1)	0.94 (0.23)	0.97 (0.17)	0.84 (0.36)	0.92 (0.28)	0.99 (0.11)	0.96 (0.20)	0.88 (0.35)
Item n.5 Attention (potential score: 0–3)	2.69 (0.69)	2.74 (0.63)	2.35 (0.95)	2.66 (0.76)	2.88 (0.33)	2.87 (0.34)	2.25 (1.16)
Item n.6 Language (potential score: 0–2)	1.76 (0.52)	1.85 (0.44)	1.53 (0.60)	1.54 (0.68)	1.81 (0.45)	1.71 (0.46)	1.75 (0.71)
Item n.7 Language (potential score: 0–1)	0.58 (0.49)	0.61 (0.49)	0.50 (0.50)	0.53 (0.50)	0.61 (0.49)	0.30 (0.47)	0.88 (0.35)
Item n.8 Abstraction (potential score: 0–2)	1.67 (0.58)	1.68 (0.57)	1.56 (0.63)	1.56 (0.62)	1.74 (0.54)	2.00 (0.00)	1.75 (0.71)
Item n.9 Delayed recall (potential score: 0–5)	2.49 (1.58)	2.67 (1.46)	1.40 (1.47)	2.68 (1.69)	2.87 (1.60)	2.65 (1.70)	2.62 (1.60)
Item n.10 Orientation (potential score: 0–6)	5.82 (0.55)	5.92 (0.31)	5.36 (1.05)	5.95 (0.22)	5.86 (0.35)	5.96 (0.21)	5.50 (0.93)

MoCA, Montreal Cognitive Assessment.

Table 3 Number (and percentage) of patients per each MoCA item score

MoCA item	N (%)						
	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5	Score 6
Item n.1 Visuospatial/executive (potential score: 0–5)	3 (0.5)	35 (5.8)	65 (10.7)	112 (18.7)	174 (29)	211 (35.2)	
Item n.2 Naming (potential score: 0–3)	4 (0.7)	3 (0.5)	36 (6)	558 (92.8)			
Item n.3 Attention (potential score: 0–2)	26 (4.3)	101 (16.8)	474 (78.9)				
Item n.4 Attention (potential score: 0–1)	33 (5.5)	567 (93.7)					
Item n.5 Attention (potential score: 0–3)	13 (2.2)	41 (6.8)	65 (10.8)	482 (80.2)			
Item n.6 Language (potential score: 0–2)	25 (4.2)	97 (16.1)	479 (79.7)				
Item n.7 Language (potential score: 0–1)	253 (42.2)	346 (57.8)					
Item n.8 Abstraction (potential score: 0–2)	34 (5.7)	131 (21.8)	436 (72.5)				
Item n.9 Delayed recall (potential score: 0–5)	104 (17.3)	60 (10.8)	109 (18.2)	157 (26.2)	103 (17.2)	67 (11.2)	
Item n.10 Orientation (potential score: 0–6)	1 (0.2)	1 (0.2)	0 (0)	3 (0.5)	13 (2.2)	60 (10.8)	522 (87)

MoCA, Montreal cognitive assessment.

Table 4 Differences among the variables in relation to the MoCA score categories

Characteristic	MoCA score category				P
	No to light CI (Scores 27–30) M (SD) or N (%)	Mild CI (Score 18–26) M (SD) or N (%)	Moderate CI (Score 10–17) M (SD) or N (%)	Severe CI (Score 0–9) M (SD) or N (%)	
Age	62.1 (12.6)	68.6 (10.3)	77.1 (9.4)	83 (4.2)	0.000
Gender					n.s.
Male	132 (31.1)	273 (64.4)	18 (4.2)	1 (0.2)	
Female	63 (36.4)	98 (56.6)	11 (6.4)	1 (0.6)	
Education					0.000
Primary School	30 (20.8)	98 (68.1)	16 (11.1)	0 (0.0)	
High School	83 (31.7)	171 (65.3)	7 (2.7)	1 (0.4)	
University	78 (44.8)	92 (52.9)	4 (2.3)	0 (0.0)	
Marital status					n.s.
Married/relationship	145 (34.3)	262 (61.9)	14 (3.3)	2 (0.5)	
Single/divorced/widowed	48 (29.4)	102 (62.6)	13 (8.0)	0 (0.0)	
CCI Score					0.025
1	78 (40.6)	107 (55.7)	7 (3.6)	0 (0.0)	
2	51 (30.5)	108 (64.7)	7 (4.2)	1 (0.6)	
3	27 (29.3)	59 (64.1)	6 (6.5)	0 (0.0)	
>4	24 (19.5)	89 (72.4)	9 (7.3)	1 (0.8)	
NYHA class					0.000
I	24 (44.4)	28 (51.9)	2 (3.7)	0 (0.0)	
II	127 (37.0)	206 (60.1)	10 (2.9)	0 (0.0)	
III	31 (18.2)	120 (70.6)	17 (10.0)	2 (1.2)	
IV	0 (0.0)	4 (100)	0 (0.0)	0 (0.0)	
EF	38.4 (12.2)	38.7 (11.8)	40.6 (12.6)	44.0 (5.6)	n.s.
6MWT score	463.3 (117.4)	385.9 (139.5)	229.3 (116.4)	163.5 (4.9)	0.000

Comparisons were performed with χ^2 or ANOVA as appropriate.
CCI, Charlson comorbidity index; EF, ejection fraction; NYHA, New York Heart Association; MoCA, Montreal cognitive assessment; 6MWT, 6 minute walking test.

and patients with HF are cared for in several health care settings (e.g. outpatient settings, rehabilitation, and private cardiology practices). Consequently, our findings provide a better and comprehensive representation of CI in patients with HF. This might have important clinical and research implications.

Sixty-two percent (*n* = 371) of our sample had mild CI. This percentage is similar to that identified by Harkness *et al.*[23] in a sample of 44 patients with HF in an outpatient setting (70%) but higher than that identified by Gallagher *et al.*,[24] where 55% of patients with HF (*n* = 124) had a score <26 on the MoCA. The percentage of patients with CI falls within the range of prior studies that have been included in systematic reviews.[10] Our finding corroborates further that CI is an important problem in patients with HF.

Looking at the MoCA scores across the six countries in which we enrolled the patients (*Table 2*), we saw significant differences across these subsamples. For example, Italian patients had the lowest score on the MoCA when compared with patients of other countries. However, Italian patients were enrolled in a rehabilitation hospital and could have been more cognitively compromised than other patients enrolled, for example, in outpatient settings, as in Sweden. Further studies with more comparable patients should be conducted to see

Table 5 Correlations among the studied variables

Variable	1	2	3	4	5	6	7	8
1. Total MoCA score	1							
2. Gender (Male = 1; Female = 2)	0.015	1						
3. Age	−0.322**	0.026	1					
4. Education	0.244**	0.000	−.118**	1				
5. Time after HF diagnosis (in months)	0.010	−0.041	0.015	−0.020	1			
6. NYHA class	−0.261**	0.107*	0.243**	−0.123**	−0.021	1		
7. Ejection fraction	−0.036	0.105*	0.171**	−0.053	−0.095	0.028	1	
8. Charlson comorbidity index score	−0.236**	−0.162**	0.221**	−0.066	0.141**	0.264**	−0.001	1
9. Six minute walk test score	0.396**	−0.125**	−0.397**	0.183**	0.052	−0.458**	−0.230**	0−.287**

Lower MoCA scores mean worse cognitive impairment; each number of the first row corresponds to the variable with the same number in the first column; and numbers in the cells are correlation coefficients.
HF, heart failure; NYHA, New York Heart Association; MoCA, Montreal cognitive assessment.
*$P < 0.05$ and
**$P < 0.01$.

Table 6 Regression analysis predicting MoCA total score and MoCA dimension scores

Variable	Total MoCA score	Visuospatial/ executive	Naming	Attention	Language	Abstraction	Delayed recall	Orientation
Gender (Male = 1; Female = 2)	0.053	−0.006	−0.093	−0.003	0.091	−0.095	0.095	0.061
Age	-0.210***	−0.166**	−0.053	−0.099	0.032	−0.076	−0.186**	−0.108#
Education	0.152**	0.168**	0.033	0.133*	0.213***	0.091	−0.070	−0.012
Time after HF diagnosis (in months)	0.023	0.042	−0.133*	0.011	−0.026	−0.079	0.033	0.081
NYHA class	0.010	−0.048	0.059	−0.063	0.018	−0.020	−0.029	0.022
Ejection fraction	0.070	0.082	0.017	0.000	0.093	0.109¥	0.043	0.050
Charlson comorbidity index score	-0.082	−0.026	0.010	−0.045	−0.072	−0.065	−0.007	−0.026
Six minute walk test score	0.311***	0.217***	0.135*	0.130*	0.249***	0.013	0.106	0.258***
R^2	0.266	0.183	0.050	0.098	0.143	0.049	0.059	0.097

Lower MoCA scores mean worse cognitive impairment. Numbers in columns are standardized betas. ¥P 0.052; #P 0.055
HF, heart failure; NYHA, New York Heart Association; MoCA, Montreal cognitive assessment.
*$P < 0.05$,
**$P < 0.01$,
***$P < 0.001$.

if CI in patients with HF might be influenced by different approaches in HF treatment and cultural factors across countries. Interestingly, we found that 28.1 % scored 0 or 1 for delayed recall (short-term memory), meaning that our population had important memory problems, which confirms other studies that found that memory and executive functions were cognitive areas particularly damaged in patients with HF.[25] This finding is important to consider when delivering patient education and when asking patients to perform self-care tasks, such as monitoring deterioration or taking medications.

In this study, we analysed sociodemographic and clinical variables independently associated with the global CI and with impairment of specific cognitive dimensions. Interestingly, we saw that older age, education, and exercise capacity were predictors of the global CI, a finding that was not observed across the specific domains. For example, time after diagnosis and exercise capacity were predictors of the naming dimension, and age was a predictor of delayed recall. To our knowledge, no prior studies have previously identified sociodemographic and clinical predictors of specific cognitive domains, and these new findings may be helpful to guide future investigations and interventions in patients with HF. For example, while patient's age predicted the visuospatial/executive domain, it was not associated with the naming domain. Interestingly, exercise capacity was associated with global CI and five out of the seven cognitive domains. This finding is important because exercise capacity could be improved in patients with HF. Prior studies have already found that physical activity was associated with better cognition in patients with HF.[26]

This study has strengths and limitations. A strength was the large multinational sample of patients with HF from multiple settings. We have given a wide description of CI in patients with HF. At the same time, our study strengths could be considered a limitation because the sample we enrolled was heterogeneous and selected with convenience procedures. Another limitation is that our study was a cross-sectional and secondary analysis with patients originally selected to evaluate the effectiveness of exergaming to improve exercise capacity in patients with HF. Even though CI was not an exclusion criterion for enrolling patients and only two patients were excluded from the study because their CI was an impediment to play with the Wii computer, we might have had a selection bias. However, the distribution of CI in our population was not different from other studies. Another limitation of our study was that we used a screening tool to evaluate CI that could be better evaluated with other tools with better sensitivity and specificity.

Our study has important practical implications because patients with HF who are more cognitively compromised have worse outcomes, such as lower self-care,[22] higher mortality,[27] and more frequent hospitalizations.[28] Our findings showed that exercise capacity, a modifiable factor, was independently associated with CI. This means that improving physical activity has the potential to improve direct (e.g. cognition) and indirect (e.g. lower mortality rates) outcomes in patients with HF. Improving physical activity in HF is advocated in the international guidelines.[1] We have also discovered from our analysis that specific cognitive domains have different predictors that may be useful to know in clinical practice. For example, a patient's older age was associated with worse delayed recall (memory) but not with abstraction. Practically, this means that older patients with HF may find it difficult to memorise the medications they have to take but not the fact that diuretics help to eliminate water from the body (Abstraction).

This study has several research implications. Since we observed different predictors for specific cognitive domains, it would be important to conduct further studies to confirm our findings. Another important implication is the use of longitudinal designs and randomized controlled trials to examine if increased physical activity is associated with improved cognition. A recent pilot study[29] found that a programme of combined aerobic exercise and cognitive training improved memory in patients with HF, but further studies are needed to clarify this association.

Acknowledgement

The following persons played a vital role in data collection. Norrköping: L Nestor, C Norrman, M Viklander, A Waldemar, RM Petterson; M Wärfman; Jönköping: E Lundberg, H Sköldbäck, M Sahlin; Linköping: A Gylling, M Huss, M Jonsson, P Wodlin, L Hjelmfors; Stockholm: E Hägglund, U Lennmark; Nyköping: E Säfström; Italy: R Corsi, G Alberto Ortali; The Netherlands: HP Brunner-La Rocca, M Spanjers, A van de Voorde, G Cleuren; Israel: S Donanhirsh, Y Navon, V Yaari B. Avraham; Germany: A Hagenow, A Kuntzsch; and United States: J Ardo, J Nguyen, M Cacciata.

Conflict of interest

None to declare

Funding

This work was supported through the Swedish National Science Council (K2013-69X-22302-01-3, 2016-01390), Swedish National Science Council/Swedish Research Council for Health, Working Life and Welfare (VR-FORTE) 2014-4100, The Swedish Heart and Lung Association E085/12, The Swedish Heart and Lung Foundation (20130340 and 20160439), the Vårdal Foundation (2014–0018), the Medical Research Council of Southeast Sweden (FORSS 474681).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. MoCA item descriptive analysis.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016; **37**: 2129–2200.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey de Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride P, McMurray J, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147–e239.
3. Heo S, Moser DK, Lennie TA, Fischer M, Kim J, Lee M, Walsh MN, Ounpraseuth S. Changes in heart failure symptoms are associated with changes in health-related quality of life over 12 months in patients with heart failure. *J Cardiovasc Nurs* 2018; **33**: 460–466.
4. Fernández-Gassó L, Hernando-Arizaleta L, Palomar-Rodríguez JA, Abellán-Pérez

MV, Hernández-Vicente Á, Pascual-Figal DA. Population-based study of first hospitalizations for heart failure and the interaction between readmissions and survival. *Rev Española Cardiol (English Ed.)* 2018; **72**: 740–748.
5. Formiga F, Moreno-Gonzalez R, Chivite D, Yun S, Franco J, Ariza-Solé A, Corbella X. Sex differences in 1-year mortality risks in older patients experiencing a first acute heart failure hospitalization. *Geriatr Gerontol Int* 2019; **19**: 184–188.
6. Łyszczarz B. Indirect costs and public finance consequences of heart failure in Poland, 2012–2015. *BMC Public Health* 2018; **18**: 1130.
7. Sterling MR, Jannat-Khah D, Bryan J, Banerjee S, McClure LA, Wadley VG, Unverzagt FW, Levitan EB, Goyal P, Peterson JC, Manly JJ. The prevalence of cognitive impairment among adults with incident heart failure: the reasons for geographic and racial differences in stroke (REGARDS) study. *J Card Fail* 2018; **25**: 130–136.
8. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray J, Quinn TJ. Cognitive impairment and heart failure: systematic review and meta-analysis. *J Card Fail* 2017; **23**: 464–475.
9. Huynh QL, Negishi K, Blizzard L, Saito M, de Pasquale CG, Hare JL, Leung D, Stanton T, Sanderson K, Venn AJ, Marwick TH. Mild cognitive impairment predicts death and readmission within 30 days of discharge for heart failure. *Int J Cardiol* 2016; **221**: 212–217.
10. Ampadu J, Morley JE. Heart failure and cognitive dysfunction. *Int J Cardiol* 2015; **178**: 12–23.
11. Fendler TJ, Spertus JA, Gosch KL, Jones PG, Bruce JM, Nassif ME, Flint KM, Dunlay SM, Allen LA, Arnold SV. Incidence and predictors of cognitive decline in patients with left ventricular assist devices. *Circ Cardiovasc Qual Outcomes* 2015; **8**: 285–291.
12. Ghanbari A, Moaddab F, Salari A, Kazemnezhad Leyli E, Sedghi Sabet M, Paryad E. The study of cognitive function and related factors in patients with heart failure. *Nurs midwifery Stud* 2013; **2**: 34–38.
13. Alosco ML, Spitznagel MB, Cohen R, Sweet LH, Hayes SM, Josephson R, Hughes J, Gunstad J. Decreases in daily physical activity predict acute decline in attention and executive function in heart failure. *J Card Fail* 2015; **21**: 339–346.
14. Pulignano G, Del Sindaco D, De Lenarda A, Tinti MD, Tarantini L, Cioffi G, Tolone S, Pero G, Minardi G. Chronic renal dysfunction and anaemia are associated with cognitive impairment in older patients with heart failure. *J Cardiovasc Med* 2014; **15**: 481–490.
15. Hanon O, Vidal JS, de Groote P, Galinier M, Isnard R, Logeart D, Komajda M. Prevalence of memory disorders in ambulatory patients aged >/=70 years with chronic heart failure (from the EFICARE study). *Am J Cardiol* 2014; **113**: 1205–1210.
16. Jaarsma T, Klompstra L, Ben Gal T, Boyne J, Vellone E, Bäck M, Dickstein K, Fridlund B, Hoes A, Piepoli MF, Chialà O, Mårtensson J, Strömberg A. Increasing exercise capacity and quality of life of patients with heart failure through Wii gaming: the rationale, design and methodology of the HF-Wii study; a multicentre randomized controlled trial. *Eur J Heart Fail* 2015; **17**: 743–748.
17. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695–699.
18. Athilingam P, King KB, Burgin SW, Ackerman M, Cushman LA, Chen L. Montreal cognitive assessment and mini-mental status examination compared as cognitive screening tools in heart failure. *Hear Lung* 2011; **40**: 521–529.
19. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.
20. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; **132**: 919–923. http://www.ncbi.nlm.nih.gov/pubmed/3978515 (12 January 2019).
21. Rostagno C, Olivo G, Comeglio M, Boddi V, Banchelli M, Galanti G, Gensini GF. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail* 2003; **5**: 247–252.
22. Hjelm CM, Broström A, Riegel B, Årestedt K, Strömberg A. The association between cognitive function and self-care in patients with chronic heart failure. *Hear Lung J Acute Crit Care* 2015; **44**: 113–119.
23. Harkness K, Demers C, Heckman GA, McKelvie RS. Screening for cognitive deficits using the Montreal cognitive assessment tool in outpatients ≥65 years of age with heart failure. *Am J Cardiol* 2011; **107**: 1203–1207.
24. Gallagher R, Sullivan A, Burke R, Hales S, Gillies G, Cameron J, Saliba B, Tofler G. Mild cognitive impairment, screening, and patient perceptions in heart failure patients. *J Card Fail* 2013; **19**: 641–646.
25. Kim J, Shin M-S, Hwang SY, Park E, Lim YH, Shim JL, Kim SH, Kim YH, An M. Memory loss and decreased executive function are associated with limited functional capacity in patients with heart failure compared to patients with other medical conditions. *Heart Lung* 2018; **47**: 61–67.
26. Alosco ML, Brickman AM, Spitznagel MB, Sweet LH, Josephson R, Griffith EY, Narkhede A, Hughes J, Gunstad J. Daily physical activity is associated with subcortical brain volume and cognition in heart failure. *J Int Neuropsychol Soc* 2015; **21**: 851–860.
27. Lan H, Hawkins LA, Kashner M, Perez E, Firek CJ, Silvet H. Cognitive impairment predicts mortality in outpatient veterans with heart failure. *Hear Lung* 2018; **47**: 546–552.
28. Sterling MR, Safford MM, Goggins K, Nwosu SK, Schildcrout JS, Wallston KA, Mixon AS, Rothman RL, Kripalani S. Numeracy, health literacy, cognition, and 30-day readmissions among patients with heart failure. *J Hosp Med* 2018; **13**: 145–151.
29. Gary RA, Paul S, Corwin E, Butts B, Miller AH, Hepburn K, Williams B, Waldrop-Valverde D. Exercise and cognitive training as a strategy to improve neurocognitive outcomes in heart failure: a pilot study. *Am J Geriatr Psychiatry.* 2019; **27**: 809–819.