European Heart Journal - Quality of Care and Clinical Outcomes (2022) **0**, 1–10
https://doi.org/10.1093/ehjqcco/qcab086

ORIGINAL ARTICLE

Cardiac rehabilitation for patients with heart failure: association with readmission and mortality risk

Lau Caspar Thygesen[1,*], Line Zinckernagel[1], Hasnain Dalal[2,3], Kenneth Egstrup[4], Charlotte Glümer[5], Morten Grønbæk[1], Teresa Holmberg[1], Lars Køber[6], Karen la Cour[7], Anne Nakano[8], Claus Vinther Nielsen[9,10,11], Kirstine Lærum Sibilitz[6], Janne Schurmann Tolstrup[1], Ann Dorthe Zwisler[12] and Rod S Taylor[1,13]

[1]National Institute of Public Health, University of Southern Denmark, Studiestræde 6, DK-1455 Copenhagen, Denmark; [2]University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, UK; [3]Primary Care Research Group, University of Exeter Medical School, St Luke's Campus, Exeter, UK; [4]Department of Cardiovascular Research, Odense University Hospital, Svendborg, Denmark; [5]Center for Diabetes in the City of Copenhagen, Copenhagen, Denmark; [6]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [7]Department of Public Health, University of Southern Denmark, Odense, Denmark; [8]The Danish Clinical Registries (RKKP), Aarhus. Denmark; [9]Institute of Public Health, Aarhus University, Aarhus, Denmark; [10]DEFACTUM, Central Denmark Region, Aarhus, Denmark; [11]Regional Hospital West Jutland, Herning, Denmark; [12]REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital and University of Southern Denmark, Nyborg, Denmark; and [13]Institute of Health and Well Being, University of Glasgow, Glasgow, UK

Received 16 September 2021; revised 8 November 2021; editorial decision 15 November 2021; accepted 17 November 2021; online publish-ahead-of-print 30 November 2021

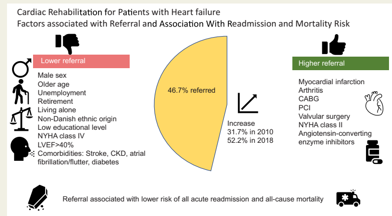
Aims To examine the temporal trends and factors associated with national cardiac rehabilitation (CR) referral and compare the risk of hospital readmission and mortality in those referred for CR versus no referral.

Methods and results This cohort study includes all adult patients alive 120 days from incident heart failure (HF) identified by the Danish Heart Failure Registry (n = 33 257) between 2010 and 2018. Multivariable logistic regression models were used to assess the association between CR referral and patient factors and acute all-cause hospital readmission and mortality at 1 year following HF admission. Overall, 46.7% of HF patients were referred to CR, increasing from 31.7% in 2010 to 52.2% in 2018. Several factors were associated with lower odds of CR referral: male sex [odds ratio (OR): 0.85; 95% confidence interval: 0.80–0.89], older age, unemployment, retirement, living alone, non-Danish ethnic origin, low educational level, New York Heart Association (NYHA) class IV vs. I (OR: 0.75; 0.60–0.95), left ventricular ejection fraction >40%, and comorbidity (stroke, chronic kidney disease, atrial fibrillation/flutter, and diabetes). Myocardial infarction, arthritis, coronary artery bypass grafting, percutaneous coronary intervention, valvular surgery, NYHA class II, and use of angiotensin-converting enzyme inhibitors were associated with higher odds of CR referral. CR referral was associated with lower risk of acute all-cause readmission (OR: 0.92; 0.87–0.97) and all-cause mortality (OR: 0.65; 0.58–0.72).

Conclusion Although increased over time, only one in two HF patients in Denmark were referred to CR in 2018. Strategies are needed to reduce referral disparities, focusing on subgroups of patients at highest risk of non-referral.

* Corresponding author. Tel: +45 65507771, Email: lct@sdu.dk

Graphical Abstract Factors associated with referral to cardiac rehabilitation.



Keywords Heart failure • Cardiac rehabilitation • Secondary prevention • Guideline adherence • Registries

Introduction

Heart failure (HF) is a major cause of morbidity, mortality, and healthcare costs.[1,2] It affects around 1–2% of the adult population in developed countries,[1,2] and accounts for 1–3% of the total healthcare expenditure in North America, Western Europe, and Latin America.[3,4] People with HF experience marked reductions in their exercise capacity, which is associated with reduced quality of life and adverse clinical outcomes.[5] The prognosis of HF is poor, with high hospitalization and mortality rates.[1,2] In the USA, HF results in ~1.0 million hospitalizations annually.[6]

Meta-analyses of randomized controlled trials (RCTs) have demonstrated that exercise-based cardiac rehabilitation (CR) improves health-related quality of life, reduces hospitalizations, and is cost-effective.[7–12] The effect on mortality is, however, equivocal.[7,13] Accordingly, the current guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology recommend the provision of exercise-based CR (class I, level A evidence) for the management of HF.[1,14]

Despite this evidence and strong guideline recommendation, CR referral remains suboptimal among patients with HF.[15–22] However, previous studies of CR referral and access are typically based on data sets from single or a small number of centres and therefore likely to be prone to bias and lack external generalizability and statistical power. Therefore, we undertook a national register-based study including all HF patients admitted to a hospital in Denmark in 2010–18 to (1) examine the temporal trends and factors associated with CR referral and (2) compare the risk of acute all-cause readmission and mortality in those referred for CR with the risk for those not referred.

Methods

Study design

This was a national register-based cohort study of all adult HF patients admitted to a hospital in Denmark in the period 2010–18.

Setting

The Danish healthcare system is universal with the goal of equal access to healthcare for all 5.8 million inhabitants. The majority of healthcare services, including CR, is financed by general taxes.[23] The Danish Health Authority released the first national guidelines on CR with exercise training in 1997,[24] and HF became an indication for CR in 2004.[25] According to national guidelines, patients should be referred from the hospital to CR either at the hospital or at the municipalities no later than at the time of discharge.[26]

Data sources

The Danish Heart Failure Registry (DHFR) is a nationwide register established in 2003 as a quality improvement initiative aimed at monitoring and improving quality of care for patients with specific severe diseases, including HF.[27] Reporting is mandatory for all hospital departments and outpatient cardiology clinics treating patients with HF. The register holds information on all adult patients (≥18 years old) with incident HF and provides information on referral to exercise-based CR and clinical factors. Less severe cases may not be recorded in the DHFR if only treated in general practice.[27]

The Civil Registration System includes all Danish residents and provides a person identification number to all residents,[28] which is used by all public authorities and registers, making linkage possible.

The Danish National Patient Register includes all inpatient hospital contacts since 1977 and also emergency room and outpatient contacts since 1995.[29] Each registration has information on primary and secondary diagnoses.

The Cause of Death Register provides information on underlying and contributing causes of death.[30]

Information on socioeconomic factors was included from the Education Register[31] and the Employment Classification Module.[32]

Study population

The study population was based on the DHFR. The data set comprised 36 361 adult patients admitted with an incident primary diagnosis of HF between 1 January 2010 and 31 December 2018 since we only had information from the Danish National Patient Register until 2018.

We linked this population with the Civil Registration System and excluded those patients not in the register from 2009 to 2019 ($n = 49$) or those not in the register in the year of the heart failure diagnosis ($n = 19$). This resulted in a study population of 35 052. Since rehabilitation is implemented within 120 days of HF admission, we excluded those patients who died within 120 days from HF admission ($n = 1795$), leaving a study population of 33 257 patients.

Variables

We identified exercise-based CR referral within 120 days from HF admission by combining information from the DHFR (whether the patient was referred to or had started supervised physical training by physiotherapist) and the Danish National Patient Register (procedure codes related to physical training).[33] Information on data sources and coding of all variables is listed in Supplementary material online, *Table S1*.

Information on demographics included sex, age, calendar year, and region. Socioeconomic factors included employment status, living alone, ethnic origin, and educational level. Clinical factors included admission type (in- or outpatient), New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), comorbidities (history of myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, and diabetes mellitus), surgical interventions [coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and valvular surgery], and use of drugs [beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone antagonists/digoxin].

We included risk of acute all-cause readmission as an outcome and followed HF patients in the Danish National Patient Register for all acute admissions. We also evaluated cause-specific mortality with HF as the underlying cause of death based on the Cause of Death Register and overall mortality based on the Civil Registration System.

Statistical analyses

Descriptive statistics were reported as numbers, proportions, means, and standard deviations. Differences were tested with χ^2- and *t*-tests for categorical and continuous variables, respectably. The trend in CR referral over time was assessed using linear regression. The associations between CR referral and demographic, socioeconomic, and clinical factors were evaluated using multivariable logistic regression models adjusted for all variables (sex, age, calendar year, region, admission type, employment status, living alone, ethnic origin, educational level, NYHA class, LVEF, myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, diabetes mellitus, CABG, PCI, and valvular surgery, and use of beta blockers, ACE inhibitors, or aldosterone antagonists/digoxin) and Danish geographical regions. The main analyses were conducted among patients alive 120 days after first heart failure admission ($n = 33\ 257$). As a sensitivity analysis, we also performed multivariable logistic regression modelling based on all HF patients ($n = 35\ 052$).

The associations between CR referral and the risk of acute all-cause readmission and mortality (HF-specific and overall) were evaluated by multivariable logistic regression models. These analyses were conducted among patients alive 120 days after first HF admission and followed up for a year after admission. We included patients between 2010 and 2017 in the analyses of acute all-cause readmission and overall mortality ($n = 29\ 501$) since outcome data were available until 2018, and patients between 2010 and 2016 for cause-specific mortality ($n = 25\ 921$) since the Cause of Death Register was updated to 2017. We conducted both a model adjusted for sex and age and a model adjusted for all variables (as listed earlier). As a sensitivity analysis, we performed the analyses of acute all-cause readmission and overall mortality stratified by NYHA classes and LVEF categories.

Logistic regression model results are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). All statistics were performed using SAS version 9.4.

Ethics

The study was approved by the University of Southern Denmark (no. 10.553). According to Danish law, this study based on registers does not require formal ethical approval.

Results

Cardiac rehabilitation referral levels and trend over time

The study population included 33 257 adult patients with an incident diagnosis of HF in the period 2010–18 who survived at least 120 days after first HF admittance (*Figure 1*). Over this 9-year period 46.7% of patients with HF were referred for CR. CR referral increased from 37.7% in 2010 to 54.1% in 2017 and decreased slightly in 2018 (52.2%) (slope: 2.3%; *P*-trend <0.0001) (*Figure 2*). This trend was similar across LVEF categories (i.e. 1.8–2.5% referrals per year). However, patients with an LVEF >50% and in some periods also patients with LVEF <25% and 41–49% appeared to be referred less than others.

Factors associated with cardiac rehabilitation referral

In the age-, sex-, and region-adjusted analyses, the majority of patient demographic, socioeconomic, and clinical factors were associated with CR referral (*Table 1*).

In the all-variable-adjusted analyses, the following factors were associated with lower CR referral (see *Table 2*): male sex (OR: 0.85; 95% CI: 0.80–0.89), older age, unemployment (OR: 0.89; 0.80–0.99), retirement (OR: 0.79; 0.73–0.85), living alone (OR: 0.76; 0.72–0.80), non-Danish ethnic origin (OR: 0.85; 0.77–0.94), low educational level (e.g. basic school vs. theoretical education, OR: 0.66; 0.61–0.70), NYHA class IV vs. I (OR: 0.75; 0.60–0.95), LVEF >40%, and comorbidity [stroke (0.90; 0.83–0.97), chronic kidney disease (OR: 0.72;0.66–0.79), atrial fibrillation/flutter (OR: 0.84; 0.79–0.88), and diabetes (OR: 0.84; 0.79–0.90)].

Myocardial infarction, arthritis, CABG, PCI, valvular surgery, NYHA class II, and use of ACE inhibitors were associated with higher CR referral (*Table 2*).

Admission type (inpatient vs. outpatient) and use of beta blockers and aldosterone antagonists/digoxin were not associated with CR referral (*Table 2*).

As a sensitivity analysis, we performed the same analyses based on all HF patients, i.e. not conditioning for survival at 120 days. These analyses showed almost the same results as the main analysis (Supplementary material online, *Table S2*).

Association between cardiac rehabilitation referral and acute all-cause readmission and mortality

CR referral was associated with a reduction in the risk of acute all-cause readmission with an adjusted OR of 0.92 (95% CI: 0.87–0.97) (*Table 3*). CR referral was also associated with lower odds of overall mortality (OR: 0.65; 0.58–0.72). While similar association between CR referral and HF-specific mortality

Table 1 Comparison of patient characteristics between heart failure patients referred and not referred to cardiac rehabilitation (*N* = 33 257)

		All patients N	Not referred, N (%)	Referred, N (%)	P-value
Total		33 257	17 733 (53.3)	15 524 (46.7)	
Demographics					
Sex	Male	22 754	11 895 (52.3)	10 859 (47.7)	<0.0001
	Female	10 503	5838 (55.6)	4665 (44.4)	
Age	Mean (SD)	68.9 (12.6)	71.1 (12.7)	66.5 (12.0)	<0.0001
	18–49 years	2570	1093 (42.5)	1477 (57.5)	<0.0001
	50–59 years	4719	2048 (43.4)	2671 (56.6)	
	60–69 years	8577	4066 (47.4)	4511 (52.6)	
	70–79 years	10 288	5472 (53.2)	4816 (46.8)	
	80–89 years	6295	4382 (69.6)	1913 (30.4)	
	90+ years	808	672 (83.2)	136 (16.8)	
Region	Capital region	8441	5247 (62.2)	3194 (37.8)	<0.0001
	Zealand	7775	4023 (51.7)	3752 (48.3)	
	South Denmark	7973	4054 (50.8)	3919 (49.2)	
	Central Denmark	6563	3036 (46.3)	3527 (53.7)	
	North Jutland	2505	1373 (54.8)	1132 (45.2)	
Socioeconomics					
Employment status	In employment or self-employed	7794	3202 (41.1)	4592 (58.9)	<0.0001
	Unemployed or studying	1809	848 (46.9)	961 (53.1)	
	Retired	23 654	13 683 (57.8)	9971 (42.2)	
Living alone	No	19 130	9311 (48.7)	9819 (51.3)	<0.0001
	Yes	14 127	8422 (59.6)	5705 (40.4)	
Ethnic origin	Non-Danish	1915	1052 (54.9)	863 (45.1)	0.14
	Danish	31 342	16 681 (53.2)	14 661 (46.8)	
Educational level	Basic school	13 577	7902 (58.2)	5675 (41.8)	<0.0001
	Vocational education	12 439	6232 (50.1)	6207 (49.9)	
	Short or long theoretical education	5972	2747 (46.0)	3225 (54.0)	
	Missing	1269	852 (67.1)	417 (32.9)	
Clinical factors					
Admission type	Inpatient	12 278	7238 (59.0)	5040 (41.0)	<0.0001
	Outpatient	20 979	10 495 (50.0)	10 484 (50.0)	
NYHA	Class I	4873	2473 (50.7)	2400 (49.3)	<0.0001
	Class II	19 364	9505 (49.1)	9859 (50.9)	
	Class III	6710	3950 (58.9)	2760 (41.1)	
	Class IV	401	278 (69.3)	123 (30.7)	
	Not classified/missing	1909	1527 (80.0)	382 (20.0)	
LVEF (%)	0–24	7764	4198 (54.1)	3566 (45.9)	<0.0001
	25–35	14 284	7438 (52.1)	6846 (47.9)	
	36–40	6584	3317 (50.4)	3267 (49.6)	
	41–49	2046	1141 (55.8)	905 (44.2)	
	50+	2221	1339 (60.3)	882 (39.7)	
	Missing	358	300 (83.8)	58 (16.2)	
Comorbidities	Myocardial infarction	11 740	5376 (45.8)	6364 (54.2)	<0.0001
	Hypertension	14 456	7949 (55.0)	6507 (45.0)	<0.0001
	Chronic obstructive lung disease	5152	2965 (57.6)	2187 (42.4)	<0.0001
	Stroke	3484	2060 (59.1)	1424 (40.9)	<0.0001
	Arthritis	9384	5011 (53.4)	4373 (46.6)	0.86
	Chronic kidney disease	2495	1582 (63.4)	913 (36.6)	<0.0001
	Atrial fibrillation/flutter	11 425	6762 (59.2)	4663 (40.8)	<0.0001
	Diabetes mellitus	6012	3470 (57.7)	2542 (42.3)	<0.0001
Cardiac procedures	Coronary artery bypass grafting	2966	1382 (46.6)	1584 (53.4)	<0.0001
	Percutaneous coronary intervention	7764	3049 (39.3)	4715 (60.7)	<0.0001
	Valvular surgery	1246	573 (46.0)	673 (54.0)	<0.0001
Cardiovascular medication	Beta blockers	16 643	8531 (51.3)	8112 (48.7)	<0.0001
	ACE inhibitors	18 155	9126 (50.3)	9029 (49.7)	<0.0001
	Aldosterone antagonists/digoxin	3602	1837 (51.0)	1765 (49.0)	0.003

SD, standard deviation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; and ACE inhibitors, angiotensin-converting enzyme inhibitors.

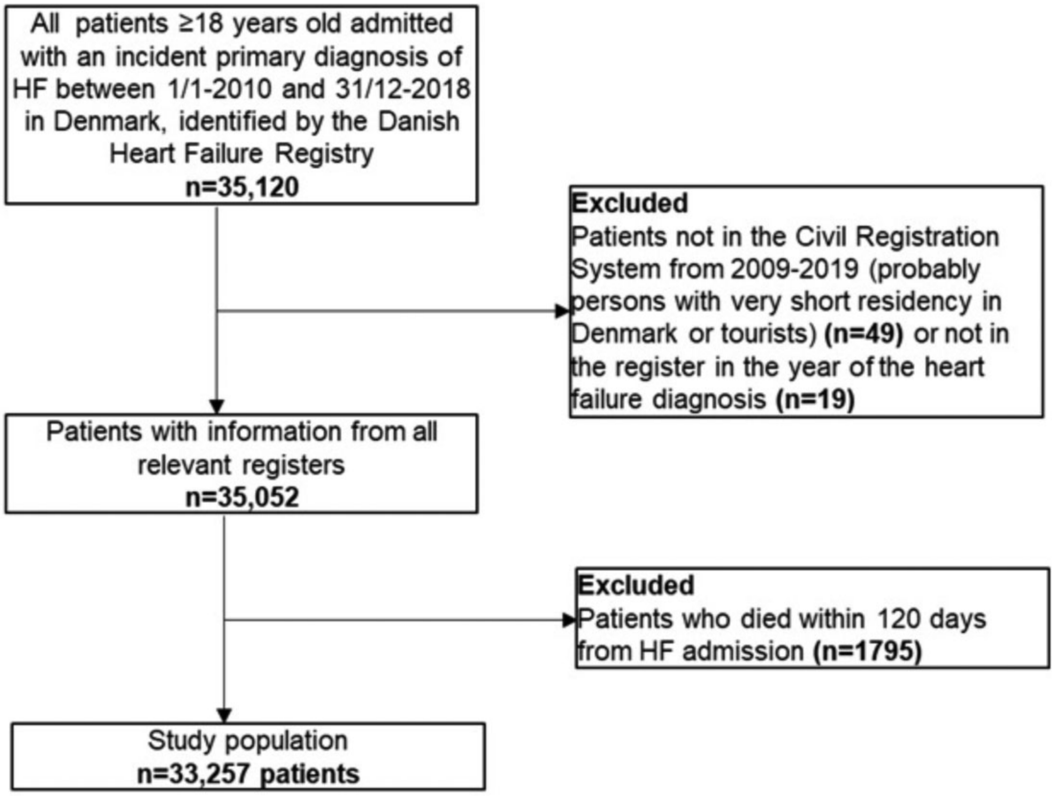


Figure 1 Flowchart depicting the derivation of the study population.

was seen, it was not statistically significant (OR: 0.66; 0.42–1.04).

As sensitivity analyses, we evaluated the risk of acute all-cause readmission and all-cause mortality stratified by NYHA classes and LVEF categories. These results showed similar results in all subgroups (see Supplementary material online, *Table S3*).

Discussion

Our study of CR referral among all adult patients in Denmark admitted with incident HF between 2010 and 2018 presents several noteworthy findings. First, there was an increasing trend in CR referral during the period, yet only one in two patients was referred to CR in 2018. Second, major disparities in CR referral were observed across different demographic, socioeconomic, and clinical subgroups. Third, CR was associated with lower odds of acute all-cause readmission, HF-specific mortality (not statistically significant), and overall mortality. Our results underline the urgent need for improving levels of CR referral and reduce the disparities in CR access by targeting patient subgroups at high risk of not being referred, such as patients with older age, those who are living alone, those with a low educational level, those with NYHA class IV, and those with several comorbidities.

Cardiac rehabilitation referral levels

Exercise-based CR has been demonstrated to be an efficacious intervention for people with HF. The 2019 Cochrane review of 44 randomized controlled trials in 5783 HF patients showed that participation in CR results in a reduction in all-cause hospitalization (relative risk 0.70, 95% CI: 0.60–0.83) and a clinically meaningful improvement in health-related quality of life (Minnesota Living with Heart Failure Questionnaire mean difference: −7.1; 95% CI: −10.5 to −3.7).[7] In spite of this evidence and the strong recommendation by current clinical guidelines,[1,14,26] our study shows that only one in two patients was referred in 2018. Considerably lower levels of CR referral have been reported in other country settings. For example, in the USA and UK only 10–13% of HF patients are referred to CR.[18,22] Moreover, the Exercise Training in Heart Failure (ExtraHF) survey of 172 European cardiac centres across 41 European countries (78 514 HF patients) found that an exercise CR programme was lacking in 40% of the centres with regional differences (23–64%).[17] Lack of national and local guidelines and inadequate insurance coverage for HF patients were highlighted as explanations in these studies. The higher CR referral figures in Denmark likely reflect universal healthcare coverage and two key national initiatives, i.e. regular updates of the national guidelines on CR (2013 and 2018), that may have led to an increase in referral physician awareness of the evidence base of CR, together with the

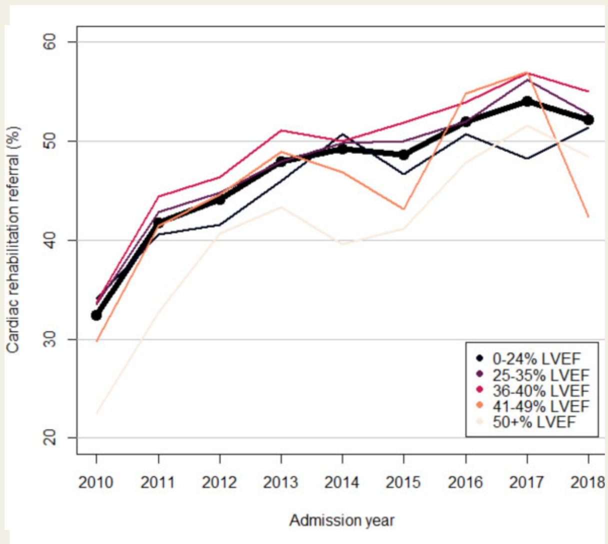


Figure 2 Temporal trends in cardiac rehabilitation referral among patients with heart failure, across four left ventricular ejection fraction categories. The bold black line is the temporal trend among all patients. LVEF, left ventricular ejection fraction.

implementation of the DHFR from 2003, an initiative aimed at monitoring and improving the quality of care. Nevertheless, although there was a rising trend in the proportion of patients with HF being referred for CR, we demonstrated a persistent gap between the national guideline recommendation and clinical practice.

Factors associated with cardiac rehabilitation referral

The barriers to CR access and specifically referral among HF patients are potentially complex and may include organizational (e.g. automated referral systems), clinician-level (e.g. lack of knowledge), and patient-level factors.[34] Our study focuses on patient-level factors.

Patient socioeconomic factors, including non-Danish ethnic origin, living alone, unemployment, retirement, and lower educational level were independently associated with lower referral, demonstrating social inequality in CR referral. Similar disparities have been found in other cardiac groups,[35,36] and our study confirms the results to be consistent in HF patients even in a country with universal healthcare coverage. Contrary to previous studies,[15,18] male sex was associated with lower CR referral.

Myocardial infarction as well as CABG, PCI, and valvular surgery was associated with higher CR referral. This was expected because these are more traditional indications for CR, and other studies have similarly demonstrated relatively higher CR among such cardiac groups.[15,16,18] In the Netherlands, 29% of patients with acute coronary syndrome and/or a cardiac procedure participated in CR, compared with 3% of HF patients,[15] and the European Cardiac Rehabilitation Registry and Database (EuroCaReD) study, with 2054 CR patients across 12 European countries, found that only 4% were admitted to CR due to HF.[16] Patients with reduced ejection fraction [HFrEF, ejection fraction (EF) ≤40%] were also more likely to be referred to CR in our study, although international and national guidelines recommend CR to HF patients, regardless of EF.[1,14,26,37] There is increasing evidence that exercise training in HF patients with preserved ejection fraction (HFpEF) has positive effects on exercise capacity, and quality of life,[8,11,12,14] but US Medicare coverage for CR to HF patients is, for instance, still restricted to HFrEF (Heart failure with reduced ejection fraction).[38] Patients with HFpEF may be increasingly important since it is the fastest growing form of HF.[14] Please note that the proportion of patients with an EF >40% (HFpEF/HFmrEF) is 13% in our study population. This indicates that this patient group is not recorded in the DHFR to the same extent as the HFrEF, since it has been estimated that ∼50% of HF patients have HFpEF/HFmrEF.[1] This may be due to a weaker evidence base for pharmacological treatment of this patient group.[1]

Older patients, patients with comorbidity (stroke and chronic kidney disease, atrial fibrillation/flutter, and diabetes), and patients with severe HF symptoms were associated with lower CR referral, indicating that healthcare professionals may perceive this group to be less likely to benefit from CR. Other studies have also found that comorbidity is associated with lower referral and CR uptake.[15,18] It has previously been suggested that physicians who incorporate evidence-based pharmacological treatment are more likely to refer patients to CR.[18] This was, nevertheless, only the case for one out of three cardiovascular medications in our study.

Cardiac rehabilitation referral and acute all-cause readmission and all-cause mortality

We found that CR referral was associated with lower odds of acute all-cause readmissions, HF-related mortality (not statistically significant), and all-cause mortality. While our findings are in accordance with previous observational analyses of improvements in admissions and survival with CR following acute coronary syndrome and post-revascularisation,[39–42] there have been few such analyses in HF. One study found in line with our results that CR participation is associated with an all-cause mortality risk reduction of 28% among HF patients,[43] and another study showed larger estimates, with 42% lower odds of all-cause mortality and 26% lower odds of hospitalization.[44] In interpreting these results, it is important to consider the observational design and risk of bias. We uniquely utilize nationwide data and used multivariable analyses including many covariates, but still need to acknowledge especially the risk of confounding by indication. RCTs have similarly demonstrated that exercise-based CR reduces hospitalizations,[7] but have not been able to demonstrate lowered mortality in HF patients.[7,13]

Clinical and health policy implications

Our findings underline the need for improving CR referral. Strategies to promote CR referral are needed to improve access to CR, and it is paramount to address the disparities in CR referral, not least because the incidence of HF is higher and prognosis poorer in many of the subgroups associated with low CR referral.[2,45] Moreover, the recent meta-analysis (ExTraMATCH II) showed that the benefits of CR are consistent across HF patient subgroups (age, sex, ethnicity, NYHA class, ischaemic aetiology, ejection fraction, and baseline exercise capacity).[8] Raising healthcare professionals' awareness about

Table 2 Association between patient-level factors and cardiac rehabilitation referral within 120 days of incident heart failure admission (*N* = 33 257)

		Odds ratio (95% CI)[a]	Odds ratio (95% CI)[b]	*P*-value[c]
Demographics				
Sex	Male	1.00 (0.95–1.05)	0.85 (0.80–0.89)	<0.0001
	Female	1.00 (ref.)	1.00 (ref.)	
Age	18–49 years	1.54 (1.41–1.68)	1.35 (1.21–1.51)	<0.0001
	50–59 years	1.48 (1.38–1.59)	1.26 (1.15–1.38)	
	60–69 years	1.26 (1.19-1.34)	1.16 (1.09-1.23)	
	70–79 years	1.00 (ref)	1.00 (ref)	
	80–89 years	0.50 (0.46-0.53)	0.55 (0.51-0.59)	
	90+ years	0.23 (0.19-0.28)	0.34 (0.28-0.41)	
Region	Capital region	1.00 (ref.)	1.00 (ref.)	<0.0001
	Zealand	1.53 (1.43–1.63)	1.40 (1.31–1.50)	
	South Denmark	1.60 (1.50–1.70)	1.47 (1.38–1.58)	
	Central Denmark	1.95 (1.82–2.08)	1.90 (1.77–2.04)	
	North Jutland	1.38 (1.25–1.51)	1.44 (1.30–1.59)	
Socioeconomics				
Employment status	In employment or self-employed	1.00 (ref.)	1.00 (ref.)	<0.0001
	Unemployed or studying	0.77 (0.70–0.86)	0.89 (0.80–0.99)	
	Retired	0.69 (0.64–0.74)	0.79 (0.73–0.85)	
Living alone	No	1.00 (ref.)	1.00 (ref.)	<0.0001
	Yes	0.70 (0.67–0.73)	0.76 (0.72–0.80)	
Ethnic origin	Danish	1.00 (ref.)	1.00 (ref.)	0.002
	Non-Danish	0.82 (0.74–0.90)	0.85 (0.77–0.94)	
Educational level	Basic school	0.67 (0.62–0.71)	0.66 (0.61–0.70)	<0.0001
	Vocational education	0.83 (0.78–0.89)	0.79 (0.74–0.85)	
	Short or long theoretical education	1.00 (ref.)	1.00 (ref.)	
Clinical factors				
Admission type	Inpatient	0.74 (0.71–0.78)	0.99 (0.94–1.05)	0.82
	Outpatient	1.00 (ref.)	1.00 (ref\.)	
NYHA	Class I	1.00 (ref.)	1.00 (ref.)	<0.0001
	Class II	1.18 (1.11–1.26)	1.26 (1.17–1.34)	
	Class III	0.87 (0.80–0.94)	1.03 (0.94–1.11)	
	Class IV	0.57 (0.46–0.71)	0.75 (0.60–0.95)	
	Not classified/ missing	0.33 (0.29–0.37)	0.48 (0.42–0.55)	
LVEF	0–24	0.88 (0.83–0.93)	1.01 (0.95–1.08)	<0.0001
	25–35	1.00 (ref.)	1.00 (ref.)	
	36–40	1.05 (0.99–1.11)	0.96 (0.91–1.03)	
	41–49	0.84 (0.77–0.93)	0.88 (0.80–0.97)	
	50+	0.72 (0.66–0.79)	0.73 (0.66–0.81)	
Comorbidities	Myocardial infarction	1.66 (1.59–1.74)	1.22 (1.15–1.30)	<0.0001
	Hypertension	0.96 (0.92–1.01)	0.97 (0.92–1.02)	0.26
	Chronic obstructive lung disease	0.86 (0.81–0.92)	0.95 (0.89–1.01)	0.10
	Stroke	0.84 (0.78–0.91)	0.90 (0.83–0.97)	0.008
	Arthritis	1.10 (1.05–1.16)	1.11 (1.06–1.17)	<0.0001
	Chronic kidney disease	0.68 (0.63–0.74)	0.72 (0.66–0.79)	<0.0001
	Atrial fibrillation/flutter	0.78 (0.75–0.82)	0.84 (0.79–0.88)	<0.0001
	Diabetes mellitus	0.79 (0.75–0.84)	0.84 (0.79–0.90)	<0.0001
Cardiac procedures	Coronary artery bypass grafting	1.41 (1.31–1.53)	1.33 (1.22–1.45)	<0.0001
	Percutaneous coronary intervention	2.04 (1.93–2.15)	1.73 (1.62–1.86)	<0.0001
	Valvular surgery	1.46 (1.30–1.64)	1.49 (1.32–1.69)	<0.0001
Cardiovascular medication	Beta blockers	1.19 (1.14–1.25)	0.98 (0.92–1.03)	0.37
	ACE inhibitors	1.30 (1.24–1.36)	1.13 (1.08–1.20)	<0.0001
	Aldosterone antagonists/digoxin	1.09 (1.02–1.17)	1.02 (0.95–1.10)	0.58

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
[a]Adjusted for age, sex, and calendar year.
[b]Adjusted for age, sex, calendar year, and other covariates.
[c]*P*-value from type-3 test in model 2.

Table 3 Association between cardiac rehabilitation referral and risk of acute all-cause readmission and mortality

	# Patients	Cases (%)	OR (95% CI)[a]	OR (95% CI)[b]
Acute all-cause readmission (*n* = 29 501)				
No CR referral	15 938	5265 (33.0)	1.00 (ref.)	1.00 (ref.)
CR referral	13 563	3669 (27.1)	0.83 (0.79–0.87)	0.92 (0.87–0.97)
Heart failure specific mortality (*n* = 25 921)				
No CR referral	14 294	103 (0.7)	1.00 (ref.)	1.00 (ref.)
CR referral	11 627	26 (0.2)	0.48 (0.31–0.75)	0.66 (0.42–1.04)
All-cause mortality (29 501)				
No CR referral	15 938	1279 (8.0)	1.00 (ref.)	1.00 (ref.)
CR referral	13 563	479 (3.5)	0.54 (0.49–0.61)	0.65 (0.58–0.72)

OR, odds ratio; CI, confidence interval; and CR, cardiac rehabilitation.
[a] Logistic regression model adjusted for sex and age.
[b] Logistic regression model adjusted for sex, age, calendar year, region, employment status, living alone, ethnic origin, educational level, admission type, New York Heart Association class, left ventricular ejection fraction (%), myocardial infarction, hypertension, chronic obstructive lung disease, stroke, arthritis, chronic kidney disease, atrial fibrillation/flutter, diabetes mellitus, coronary artery bypass grafting, percutaneous coronary intervention, valvular surgery, and use of beta blockers, angiotensin-converting enzyme inhibitors or aldosterone antagonists/digoxin.

guideline recommendations, the benefits of CR in HF, and current disparities in referral may be effective, as well as implementation of automatic referral systems. A recent study has, for instance, shown that an opt-out CR referral pathway that automatically identifies eligible patients and notifies staff was associated with a significant increase in referrals.[46] Moreover, it is well known that a large proportion of cardiac patients referred to CR do not participate.[47] Travelling time and cost to a rehabilitation centre, dislike of group exercise, and inconvenient timings (e.g. within working hours) are all barriers to participation.[48] This calls for utilization of alternative methods of CR delivery such as home-based and virtual approaches.[49] Home-based CR has similar benefits to centre-based CR in terms of health-related quality of life, all-cause readmissions, and cost.[50]

Limitations

Our nationwide study has several strengths also in comparison with previous analyses: high external validity, large sample size, no loss to follow-up, and access to a wide range of patient-level factors potentially associated with CR referral.

However, we recognize that our study has limitations. First, by focusing on CR referral we do not know how many of those referred attended CR. As it is not currently mandatory for municipalities (only for hospitals) to register information on CR participation, this information is not comprehensively available in Danish health registers. Second, our analysis may have underestimated the 'appropriate referral' proportion as it includes HF patients in the denominator who might have been deemed unsuitable for CR. The registration of referral to exercise-based CR is mandatory to all hospitals treating HF patients. In addition, thorough efforts are made to ensure data validity by conducting regular multidisciplinary audits, which include evaluation of completeness of patient registration against hospital discharge registers. Third, since this is an observational study, confounding cannot be ruled out, even though we had access to extensive patient information to reduce the risk of confounding. Fourth, the results of this national study may not be generalizable to other international healthcare settings. Finally, although our analysis predates the onset of the COVID-19 pandemic, global reductions in healthcare access over the last years underscore the importance of our findings in informing future improvements in CR access.

Conclusions

Although CR referral for patients admitted with heart failure in Denmark has increased over time, our data from 2018 show that only one in two HF patients are referred to CR. We identified important disparities in CR referral linked to particularly patient demographic, socioeconomic, and clinical characteristics. CR referral is associated with lower odds in acute all-cause readmission and mortality. These findings underline the urgent need for strategies to promote CR referral to improve access to CR, especially in those patient groups at highest risk of not being referred.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Acknowledgements

The authors thank the staff of the hospital departments caring for patients with heart failure. Their continuous effort and contribution in the collection of data to the Danish Heart Failure Registry are making studies like this possible.

Funding

Danish Heart Foundation (grant number: 20-R145-A9654-22157).

Author contributions

L.C.T., K.E., M.G., K.I.C., A.N., A.D.Z., and R.S.T. designed and conceptualized the study. L.C.T. analysed the data in close collaboration with all authors. L.C.T., L.Z., and R.S.T. drafted the first version of the paper. All the authors interpreted the data and contributed to the development of the paper, including critical revision and drafting for important intellectual content. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: L.Z. reports grants from the Danish Heart Foundation during the conduct of the study. L.K. reports personal fees from speaker honorariums from Novo, Novartis, AstraZeneca, and Boehringer, outside the submitted work. R.S.T. reports grants from DK:REACH-HF during the conduct of the study, grants from the REACH-HFpEF trial, and grants from the SCOT:REACH-HF trial, outside the submitted work. The other authors declare no conflict of interest.

Data availability

Data are linked to administrative and research registers and can be accessed through affiliation with the University of Southern Denmark. Other researchers can apply for the same data through Statistics Denmark and the Danish Clinical Registries.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW *et al.* Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation* 2021;**143**:e254–e743.
3. Metra M, Teerlink JR. Heart failure. *Lancet North Am Ed* 2017;**390**:1981–1995.
4. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S *et al.* Heart failure: preventing disease and death worldwide. *ESC Heart Fail* 2014;**1**:4–25.
5. Working Group on Cardiac Rehabilitation & Exercice Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise training in chronic heart failure patients. *Eur Heart J* 2001;**22**:125–135.
6. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. *JAMA* 2020;**324**:488–504.
7. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H *et al.* Exercise-based rehabilitation for heart failure: Cochrane systematic review, meta-analysis, and trial sequential analysis. *JACC Heart Fail* 2019;**7**:691–705.
8. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O *et al.* Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol* 2019;**73**:1430–1443.
9. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart* 2018;**104**:1403–1410.
10. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2016;**23**: 78–85.
11. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D *et al.* Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail* 2015;**8**:33–40.
12. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019;**24**:535–547.
13. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ *et al.* Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
14. Yancy CW, Jessup M, Bozkurt B, Butler J, Jr Casey DE, Drazner MH *et al.* 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.
15. van Engen-Verheul M, de Vries H, Kemps H, Kraaijenhagen R, de Keizer N, Peek N *et al.* Cardiac rehabilitation uptake and its determinants in the Netherlands. *Eur J Prev Cardiol* 2013;**20**:349–356.
16. Benzer W, Rauch B, Schmid JP, Zwisler AD, Dendale P, Davos CH *et al.* Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. *Int J Cardiol* 2017;**228**:58–67.
17. Piepoli MF, Binno S, Coats AJS, Cohen-Solal A, Corrà U, Davos CH *et al.* Regional differences in exercise training implementation in heart failure: findings from the Exercise Training in Heart Failure (ExTraHF) survey. *Eur J Heart Fail* 2019;**21**:1142–1148.
18. Golwala H, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL *et al.* Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from get with the guidelines-heart failure registry. *J Am Coll Cardiol* 2015;**66**:917–926.
19. Sola M, Thompson AD, Coe AB, Marshall VD, Thomas MP, Prescott HC *et al.* Utilization of cardiac rehabilitation among cardiac intensive care unit survivors. *Am J Cardiol* 2019;**124**:1478–1483.
20. Dalal HM, Wingham J, Palmer J *et al.* Why do so few patients with heart failure participate in cardiac rehabilitation? A cross-sectional survey from England, Wales and Northern Ireland. *BMJ Open* 2012;**2**:e000787.
21. Buttery AK, Carr-White G, Martin FC, Glaser K, Lowton K. Limited availability of cardiac rehabilitation for heart failure patients in the United Kingdom: findings from a national survey. *Eur J Prev Cardiol* 2014;**21**:928–940.
22. National Institute for Cardiovascular Outcomes Research (NICOR). *National heart failure audit (NHFA) 2020 summary report (2018/19 data)*. Healthcare Quality Improvement Partnership (HQIP); 2019.
23. The Ministry of Health. *Healthcare in Denmark—an Overview*. København K, Denmark: Ministry of Health; 2017.
24. Zwisler AD, Traeden UI, Videbaek J, Madsend M. Cardiac rehabilitation services in Denmark: still room for expansion. *Scand J Public Health* 2005;**33**:376–383.
25. The Danish Health Authority. *Guideline on Cardiac Rehabilitation at Hospitals [Vejledning om hjerterehabilitering på sygehuse]*. Copenhagen: The Danish Health Authority; 2004.
26. The Danish Health Authority. *Anbefalinger for tværsektorielle forløb for mennesker med hjertesygdom [Guidelines on cross-sectional patient journeys for patients with heart disease]*. Copenhagen: The Danish Health Authority; 2018.
27. Schjodt I, Nakano A, Egstrup K, Cerqueira C. The Danish Heart Failure Registry. *Clin Epidemiol* 2016;**8**:497–502.
28. Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011;**39**: 22–25.
29. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;**39**:30–33.
30. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health* 2011;**39**:26–29.
31. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;**39**:91–94.
32. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011;**39**:95–98.
33. The Danish Clinical Registries (RKKP) and the Expert Panel for The Heart Failure Registry. *Yearly report for the Danish Heart Failure Registry 2019 [Dansk Hjerterehabiliteringsdatabase (DHRD). Årsrapport 2019]*. Aarhus: Regionernes Kliniske Kvalitetsudviklingsprogram; 2020.
34. Ragupathi L, Stribling J, Yakunina Y, Fuster V, McLaughlin MA, Vedanthan R. Availability, use, and barriers to cardiac rehabilitation in LMIC. *Glob Heart* 2017;**12**:323–334.
35. Hansen TB, Berg SK, Sibilitz KL, Søgaard R, Thygesen LC, Yazbeck AM *et al.* Availability of, referral to and participation in exercise-based cardiac rehabilitation after heart valve surgery: results from the national CopenHeart survey. *Eur J Prev Cardiol* 2015;**22**:710–718.
36. Li S, Fonarow GC, Mukamal K, Xu H, Matsouaka RA, Devore AD *et al.* Sex and racial disparities in cardiac rehabilitation referral at hospital discharge and gaps in long-term mortality. *J Am Heart Assoc* 2018;**7**:e008088.
37. The Danish Health Authority. *National klinisk retningslinje for hjerterehabilitering 2013 [National clinical guidelines on cardiac rehabilitation 2013]*. Copenhagen: The Danish Health Authority; 2015.
38. United Healthcare Medicare Advantage. *Cardiac Rehabilitation Programs for Chronic Heart Failure (NCD 20.10.1)*. 2021.
39. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *Eur Heart J* 2015;**36**:1519–1528.
40. Patel DK, Duncan MS, Shah AS, Lindman BR, Greevy RA, Jr, Savage P *et al.* Association of cardiac rehabilitation with decreased hospitalization and mortality risk after cardiac valve surgery. *JAMA Cardiol* 2019;**4**:1250–1259.
41. Beatty AL, Doll JA, Schopfer DW, Maynard C, Plomondon ME, Shen H *et al.* Cardiac rehabilitation participation and mortality after percutaneous coronary intervention: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *J Am Heart Assoc* 2018;**7**:e010010.

42. Ekblom O, Cider A, Hambraeus K, Bäck M, Leosdottir M, Lönn A *et al.* Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women: results from the SWEDEHEART registry. *Eur J Prev Cardiol*; Doi: 10.1093/eurjpc/zwab083. Published online ahead of print 7 June 2021.
43. Eijsvogels TMH, Maessen MFH, Bakker EA, Meindersma E. P., van Gorp N., Pijnenburg N. *et al.* Association of cardiac rehabilitation with all-cause mortality among patients with cardiovascular disease in the Netherlands. *JAMA Netw Open* 2020;**28**:e2011686.
44. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Sankaranarayanan R, Wright DJ *et al.* Cardiac rehabilitation and all-cause mortality in patients with heart failure: a retrospective cohort study. *EJPC* 2021;**28**:1704–1710.
45. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP *et al.* Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet North Am Ed* 2018;**391**:572–580.
46. Adusumalli S, Jolly E, Chokshi NP, Gitelman Y, Rareshide CAL, Kolansky DM *et al.* Referral rates for cardiac rehabilitation among eligible inpatients after implementation of a default opt-out decision pathway in the electronic medical record. *JAMA Netw Open* 2021;**4**:e2033472.
47. Parashar S, Spertus JA, Tang F, Bishop KL, Vaccarino V, Jackson CF *et al.* Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction. *Circulation* 2012;**126**:1587–1595.
48. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, Raposeiras S, van 't Hof A, Meindersma E *et al.* Participation and adherence to cardiac rehabilitation programs. A systematic review. *Int J Cardiol* 2016;**223**:436–443.
49. Dalal HM, Doherty P, McDonagh ST, Paul K, Taylor RS. Virtual and in-person cardiac rehabilitation. *BMJ* 2021;**373**:n1270.
50. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K *et al.* Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev* 2017;**6**:CD007130.