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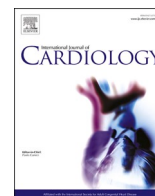
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# Optimal outcomes from cardiac rehabilitation are associated with longer-term follow-up and risk factor status at 12 months: An observational registry-based study<sup>☆</sup>

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## ABSTRACT

**Aim:** The purpose of Cardiac Rehabilitation (CR) is to promote and reduce risk factors in the short and long term, however, the latter has, to date, been poorly evaluated. We explored characteristics associated with provision and outcomes of a long-term assessment in CR.

**Method:** Data from the UK National Audit of CR between April 2015 and March 2020 was used. Programmes were selected if they had an established mechanism and routine methodology to collect the 12-month assessments. Risk factors pre and post phase II CR and at the 12-month assessment were explored; BMI  $\leq 30$ ,  $\geq 150$  min of physical activity per week, hospital anxiety and depression scale (HADS) scores  $< 8$ . The data came from 32 programmes, 24,644 patients with coronary heart disease. Patients being in at least one optimal risk factor stage throughout phase II CR (OR = 1.43 95% CI 1.28 to 1.59) or successfully reaching an optimal stage during phase II CR (OR = 1.61 95% CI 1.44 to 1.80) had an increased likelihood of being assessed at 12 months compared to those who did not. Patients being in the optimal stage upon completion of phase II CR had an increased likelihood of still being in the optimal stage at 12 months. Most prominent was BMI; (OR = 14.6 (95% CI 11.1 to 19.2) for patients reaching an optimal stage throughout phase II CR.

**Conclusion:** Being in an optimal stage upon routine CR completion could be an overlooked predictor in the provision of a long-term CR service and prediction of longer-term risk factor status.

## 1. Introduction

Routine exercise-based phase II cardiac rehabilitation (CR) services are well implemented in most European countries [1,2]. These services facilitate lifestyle behaviour change and risk factor management.

A key objective of CR is to improve the cardiovascular prognosis by reducing cardiovascular risk factors – e.g. lowering body mass index (BMI), increasing the level of physical activity and promoting psychosocial wellbeing [3,4]. Phase II CR programmes typically have a duration of 3–6 months [3]. After the completion of phase II CR, clinical standards recommend that patients undergo a post-assessment CR session and formulate a long-term health behaviour management plan and

develop personalised goals [3,4].

In randomised controlled trials (RCT), a reduction in the risk of cardiovascular mortality and myocardial infarction has been found three years after participation in CR [1]. Notwithstanding these positive implications, a translation of the benefits seen in RCTs to routine practice data is difficult due to substantial differences in patients' characteristics e.g. younger patients with fewer comorbidities have tended to be recruited to clinical trials compared to routine clinical practice [5,6]. Furthermore, a skewed distribution in referral, participation and completion rates exists in routine CR. This has the potential to considerably impact the provision of long-term CR services and associated longer-term health behaviour [7,8].

<sup>☆</sup> This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Moreover, maintaining or continuing long-term health behaviour change is challenging. As an example, only about 40% of patients remain physically active one year after CR, even though it is likely to reduce the risk of a poor cardiovascular prognosis [9,10]. In addition, evaluations of interventions applied in everyday life show that very few intensive and short-term health interventions result in long-term behaviour changes [11].

Historically, the delivery and recording of long-term CR services have been underutilised. Thus, to date, there is a sparsity of evidence and knowledge of how long-term services work in the routine setting [3,12]. Yet, the prevalence of people living with a cardiovascular disease has increased drastically over the last decade [13,14]. This, in turn, has increased the need for the healthcare system to prioritise the provision of routine long-term CR services to support long-term health behaviour [15]. So far, it is unknown to what extent patients post CR attend and complete this long-term assessment and, moreover, to what degree any behaviour change is achieved through risk factor reduction.

This paper will explore patients' characteristics associated with the provision of a long-term risk factor assessment in CR service and assess the associated level of long-term risk factor status in the population completing CR.

## 2. Method

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [16].

### 2.1. Data

Data for this project is from the National Audit of Cardiac Rehabilitation (NACR) - a UK registry with data entered by over 180 CR programmes (over 90% coverage of all programmes) [6]. The audit's goal is to monitor programmes to improve the quality-of-service delivery and outcomes in CR centres. Data entered into the audit covers the early, phase II and long-term stages of the CR pathway. In the UK, phase II CR (equal to core CR in UK) stage is an 8 to 12-week long multimodal intervention that includes exercise, education and sets goals for lifestyle change [17]. Phase II includes a pre and post assessment (at either end of phase II) where varieties of risk factor measurements are taken. Although not a standardised part of routine practice, a third assessment point measuring the long-term improvement, maintenance and change in these measures 12 months after completing CR is available. Currently, of all programmes in the UK, only 11% of all patients assessed at CR entry have long-term assessment recorded in NACR.

The recording of data into the audit is covered under section 251 of the NHS Act 2006 and submitted into the NHS Digital data storage system. Data for this study was collected for the period April 2015 to March 2020 to include the most recent data up to the emergence of COVID-19 that has altered the recording and standard running of the CR services in the UK [18].

### 2.2. Cohort of programmes

Within this study, the selection of patients was based on programmes with an established mechanism and methodology to collect the 12-month assessment. This mechanism was defined as; 1) programmes rehabilitating at least 100 patients per year or 500 over the last 5 years and 2) having a total of at least 200 or more 12-month assessments over the term. These two criteria allowed for a sufficient sample within the programmes for clustering but also ensured that patients with 12 months follow-up were standard care patients and not outliers or unique and complex individual patient pathways. Based on the inclusion criteria, 32 programmes were included (18% of all programmes).

### 2.3. Outcomes

Following the BACPR [4] and European Society of Cardiology core components [3] for phase II CR, patients are assessed prior to and at the end of the rehabilitation programme. These pre and post assessments assess different risk factors, which can be a target of the CR intervention. For this study, we were only able to assess these risk factors available in the NACR database at pre and post assessment and again at the 12-month assessment; including body mass index (BMI), physical activity level, psychosocial wellbeing measure using the Hospital Anxiety and Depression Scale (HADS) [19]. Physical activity was self-reported and based on the UK chief medical officers' guidelines for physical activity [20]. All four risk factors are stated to be of importance for phase II CR by the BACPR [4] and European Society of Cardiology core components [3].

For each risk factor, clearly defined optimal risk factor stages were used as clinical benchmarks in the data analysis; The World Health Organization (WHO) classification of obesity in adults; a BMI lower than 30 [21]. Adhering to WHO guidelines for physical activity; equal to or >150 min per week [22]. HADS anxiety and depression scores <8 [19].

### 2.4. Covariates

Patient characteristics included in the analysis were: age (mean centred), gender (male/female), ethnicity (white/non-white), partnership status (partnered/single), medical treatment status (none/ percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG)/Other treatment), comorbidity status (none/one/two or more). A measure of deprivation was included according to where patients lived, this was divided into five quintiles (Indices of Multiple Deprivation (IMD)) [23].

### 2.5. Data analysis

Descriptive statistics of mean and standard deviation (SD) were used for continuous variables and percentages and counts for the categorical variables. Independent samples *t*-tests were used to examine differences in patient characteristics between being assessed or not at 12 months after CR for continuous variables, whereas Pearson Chi-square tests (or equivalent) were used for categorical variables. A *p*-value <0.05 was considered as statistically significant.

Two sets of binary logistic regressions were built to study the association between patient characteristics and being assessed at 12 months and the likelihood of being in the optimal stage for the four outcome measures, accounting for patient characteristics.

In the first model, a factor was created based on patients' achievement during phase II CR. A three-category variable was made based on the four outcomes (BMI, Physical activity, HADS anxiety and depression), patients were either "never in an optimal stage", "In at least one optimal stage but never improved" and "made at least one improvement during CR". This allowed the analysis to account for the patient's achievement during CR in the likelihood for attending 12-month assessment.

In the second set of models, association with each of the four outcomes was assessed. For each model, a new status of their achievement was created for that outcome, e.g. BMI at 12 months had achievement for BMI pre and post CR. Patients in the optimal stage during both uptake and completion of phase II CR were categorised as "Always in the optimal stage". Whereas patients first reaching the optimal stage upon completion were categorised as "Improved throughout CR". Patients never being in the optimal stage throughout phase II CR were categorised as "Never in optimal stage".

The independent variables were entered in the models via a backward selection method involving a repeated elimination of variables with *p*-value >0.05. After model testing, estimated margins were generated to show, based on the model, the distributions of patients in

the three optimal stages for each of the four outcomes at the 12-month assessment. Estimated margins are useful to interpret the results beyond the odds ratio by showing the expected proportion of change for an adjusted and averaged population which allows for a substantive and practical presentation of the findings [24].

### 3. Results

During the five-year period, the 32 programmes that met the inclusion criteria had 62,697 patients starting CR and 42,616 that had pre and post CR assessments (68%). Study flow is illustrated in Fig. 1. Fig. 2 shows the proportion of patients in the three optimal stage categories upon CR completion for each of the four risk factors. The majority of patients across all four risk factors were always in the optimal stages (range across the four risk factors: 43 to 81%). A 25% improvement, meaning the largest improvement during phase II CR, was found for the physical activity level.

In Table 1, patient characteristics have been divided into whether the patient underwent long-term assessment at 12 months or not. All investigated variables, beside marital status ( $p = 0.076$ ), were statistically significantly different between those being assessed and those not.

Table 2 shows the association of being assessed at 12 months and patient characteristics – all insignificant factors have been removed after the backward selection process. Invasive treatment procedure and a higher number of comorbidities increased the likelihood of being assessed at 12 months. Being in the fifth IMD reduced the likelihood of a 12-month assessment by 18% (OR = 0.82 95% CI 0.77 to 0.88). Patients always being in the optimal stage in one of the four risk factors during phase II CR (OR = 1.43 95% CI 1.28 to 1.59) or patients reaching an optimal stage during phase II CR (OR = 1.61 95% CI 1.44 to 1.80) had an increased likelihood of being assessed at 12 months compared to patients never being in any of the optimal risk factors stages.

The likelihood of being in an optimal risk factor stage at 12 months upon CR completion is shown in Table 3. Patients were more likely still to be in the optimal stage at 12 months assessment if they reached an optimal stage during phase II CR compared to patients still not in the optimal stage upon completion (Table 3). This was most prominent for BMI (OR = 14.6 (95% CI 11.1 to 19.2)). Always being in an optimal stage during phase II CR showed the same pattern with BMI again being the most prominent (OR = 134.0 (95% CI 112.4 to 159.8)). Having higher levels of comorbidities, specifically three or more was the only other consistent variable across the four optimal stages (OR ranging 0.4 to 0.8).

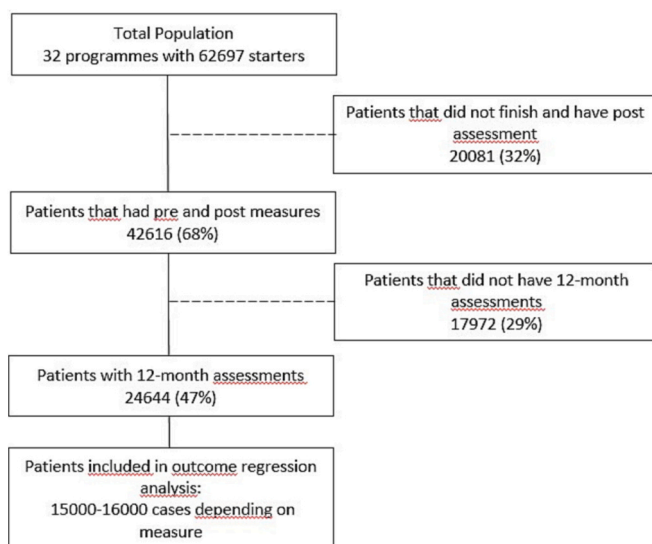


Fig. 1. Study flow.

Table 4 shows the actual distribution of patients for the four outcomes and the estimated margins generated based on the regression models to illustrate the expected proportion of change for an adjusted and averaged population. From the actual distribution, around 75% were in the optimal stage for BMI, physical activity and anxiety at 12 months. For depression, this was 85%.

Based on the model and averaging the patient population, the estimated margins showed that <8% of patients who were in the optimal stage during phase II CR had moved out of that stage at 12 months (range 4.1–7.8%). For BMI, however, 83% were still expected outside of the optimal stage at 12 months, if patients never reached the optimal stage during phase II CR. This was 42%, 50% and 56% for physical activity, anxiety and depression, respectively.

### 4. Discussion

This was the first study investigating the association between CR completion and risk factor status at 12 months post discharge. Patients undergoing an invasive treatment procedure or living with comorbidity were more likely to be assessed at 12 months whereas highly deprived patients were less likely to be assessed. Being in the optimal stage for four common cardiovascular risk factors, (BMI, physical activity level, psychosocial wellbeing, anxiety and depression), upon CR completion was the only variable consistently associated with undergoing a 12-month assessment and, in addition, associated with long-term improved cardiovascular risk factors. Our findings provide insight and evidence that will help inform the provision of long-term services and associated research.

An interesting finding of this work was that, in the routine population, over 90% of patients were always in the optimal stage and 70% who made improvements during phase II CR retained their stage at 12 months. Interestingly, between 43 and 58% of patients not in the optimal stage for depression, anxiety and physical activity had made improvements at 12 months assessment. These findings correlate with trial evidence that shows that over a longer term (3 years), CR is beneficial at achieving and maintaining secondary prevention goals [1,25,26].

Our findings are in line with The European Association of Preventive Cardiology stating that phase II CR can be extended to support long-term care needs – when appropriately selected and modulated [3]. Evidence and knowledge about the content of such routine intervention and to whom it should be provided are sparse [3,12]. Most trials testing interventions to maintain or increase patients' health behaviour after phase II CR are provided shortly after CR completion, include various components and have a short duration (<1 year) [15]. In a review by Graham et al. [15], 19 RCTs were reviewed, with twelve supporting the use of post-phase II CR interventions. These were physical activity and cognitive-behavioural components, e.g. counselling, coaching, diary logs, to change physical activity behaviour [15]. In routine CR, supporting personal goals and health benefits through long-term health behaviour management plans is also a central component [3,4]. Patients must implement the plans into regular life themselves, sometimes with only very limited support from healthcare professionals. Yet, our results suggest that what is being delivered routinely is sufficient for some patients to maintain health status a year after completion of phase II CR. Additional evidence and clinical tools are called for to better identify both those patients who can continue a long-term healthy lifestyle themselves and, in particular, those who cannot [27]. Inclusion of additional outcomes like physical function and quality of life is suggested to strengthen such classification [27].

Current evidence from interventions investigating maintenance of physical activity after completion of Phase II CR [15] suggests that implementing a 12-month assessment into all routine CR services may not necessarily be the most appropriate strategy in facilitating long-term health behaviour change. The approach is not offered shortly after completion [15], does not directly build on a theoretical framework, e.g.

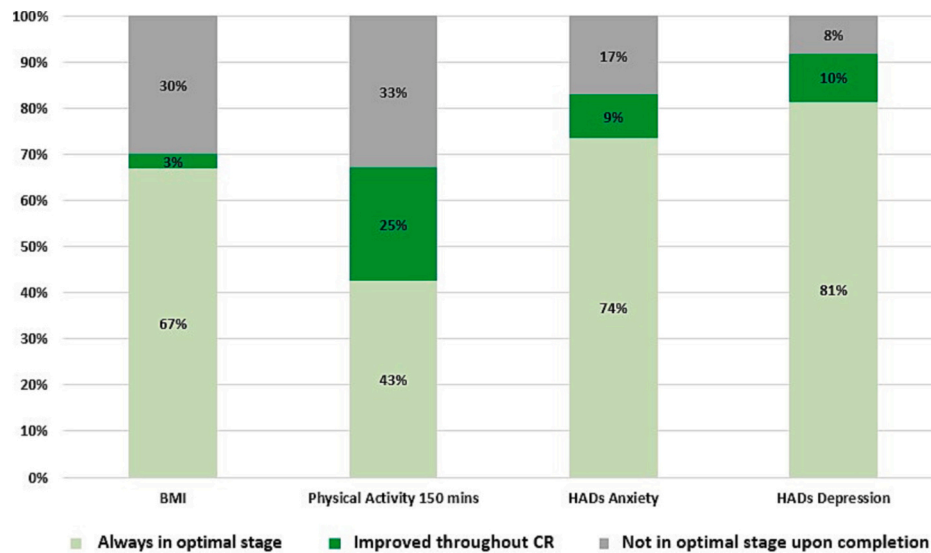


Fig. 2. The proportion of patients in each optimal stages for the four risk factors 12 weeks post core cardiac rehabilitation (CR).

Table 1

Patient characteristics and services-level factors between patients being assessed and not at 12 months after Cardiac rehabilitation (CR).

		Assessed at 12 months				Total	P-value
		No		Yes			
		Count	Row %	Count	Row %	Count	
Total Patients		17,952	42%	24,664	58%	42,616	
Age at admission(years)		Mean (SD)	Min -Max	Mean (SD)	Min -Max	Mean (SD)	Min -Max
Waiting time from Referral to Start (days)		65 (12)	18–100	66 (11)	18–101	66 (11)	18–101
Duration of Core CR (days)		36 (37)	1–365	37 (35)	1–365	37 (36)	1–365
		102 (61)	7–365	91 (57)	7–364	96 (59)	7–365
		Count	Row %	Count	Row %	Count	p-value
Gender	Male	12,951	41.7%	18,101	58.3%	31,052	0.016
	Female	4917	43.0%	6514	57.0%	11,431	
Ethnicity	White	13,836	41.3%	19,683	58.7%	33,519	<0.001
	Ethnic Minority	4116	45.2%	4981	54.8%	9097	
Employment Status	Employed/Retired	11,033	38.0%	17,972	62.0%	29,005	<0.001
	Unemployed	2708	49.1%	2805	50.9%	5513	
Marital Status	Single	2751	42.5%	3725	57.5%	6476	0.076
	Partnered	9747	41.3%	13,879	58.7%	23,626	
	None	2069	50.4%	2037	49.6%	4106	
Cardiovascular Treatment	PCI	7963	39.6%	12,149	60.4%	20,112	<0.001
	CABG	2286	41.2%	3266	58.8%	5552	
	Other Treatment	5634	43.9%	7212	56.1%	12,846	
IMD Quintiles	Lowest Quintile	2340	43.1%	3083	56.9%	5423	<0.001
	Second Quintile	2441	37.9%	4008	62.1%	6449	
	Third Quintile	3292	40.8%	4783	59.2%	8075	
	Fourth Quintile	3554	39.3%	5484	60.7%	9038	
	Fifth Quintile	4009	43.3%	5240	56.7%	9249	

Abbreviations: SD: Standard deviation, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, IMD; Indices of multiple deprivation.

a behaviour change theory that has been found superior to support patients to meet their own health behaviour goals [28–30], or take account for potential individual barriers and facilitators known to support health behaviour throughout the CR pathway [31–33]. Yet, the American Heart Association calls for more pragmatic and sustainable assessment models successfully integrated in CR [27] and stresses that risk factor assessment is of high priority - particularly in patients with a high risk profile [34]. Our results highlight the relevance of this, as patients with a poor prognosis due to e.g. comorbidity [35] were more likely to be assessed 12 months after CR completion. Unfortunately, highly deprived patients were less likely to undergo a 12-month assessment. Inequalities in behaviour related to risk factors, the cardiovascular prognosis and development of additional chronic conditions are highly associated with deprivation [36,37]. A systematic provision of long-term assessment is

thought to provide an opportunity to screen and prevent inadequate risk factor behaviour in deprived cardiovascular patient groups – but its impact needs validation in forthcoming research [27].

Being in an optimal stage for at least one of the four risk factors yielded the highest likelihood for undergoing a 12-month assessment. One explanation could be that a positive assessment upon phase II CR completion facilitates positive physiological attributes, e.g. optimism, positive affect, self-discipline and health beliefs reported in several studies to be associated with positive cardiac outcomes, risk factor behaviour and treatment adherence [38,39]. Clinical decision making has various pitfalls [40], and it may be possible that clinicians are less likely to offer a long-term assessment to patients not being in an optimal stage upon CR completion to protect them from another disappointment.

**Table 2**

The statistically significant likelihoods of being assessed at 12 months in relation to patient characteristics from a backward selection with removed factors.

	Odds ratio	95% confidence interval	p-value	
Status Post CR (base never improved)				
1. At least one improvement	1.61	1.44	1.80	<0.001
2. In at least one optimal stage, but never improved	1.43	1.28	1.59	<0.001
IMD Quintile (base First quintile)				
1. Second Quintile	1.22	1.13	1.33	<0.001
2. Fifth Quintile	0.82	0.77	0.88	<0.001
Cardiac Treatment (base no treatment)				
PCI	1.37	1.23	1.52	<0.001
CABG	1.25	1.11	1.42	<0.001
Other Treatment	1.12	1.00	1.25	0.04
Employment Status (Base Unemployed)				
Employed/Retired	1.73	1.60	1.86	<0.001
Marital Status (base Single)				
Partnered	1.07	1.00	1.15	0.04
Comorbidities (base None)				
One	1.26	1.17	1.35	<0.001
Two or More	1.41	1.29	1.55	<0.001
<b>Constant</b>	0.7560354	0.6482922	0.881685	<0.001

Abbreviations: SD: Standard deviation, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, IMD; Indices of multiple deprivation.

Being in an optimal stage upon CR completion was not only associated with undergoing a 12-month assessment but also the level of long-term risk factor and health behaviour. Based on our data, we cannot determine if this is a consequence of patients with a healthier risk factor behaviour profile being more likely to attend a 12-month assessment. It could simply be that those patients in the optimal stage upon CR completion are those with the highest adherence level to their CR programme and have higher likelihood to retain status at 12 months. Yet other patient related outcomes are also likely to interact with our findings as several barriers for sustaining adequate risk factor behaviours are known for patients living with cardiovascular diseases [32,33,38,39]. Our results, however, suggest that one of the most important predictors for long-term health behaviour is to reach an optimal stage upon routine phase II CR completion. However, further research that can confirm the findings of this study, and which includes additional risk factors, is needed before a qualified selection of patients to include in long-term

**Table 3**

The likelihood of being in an optimal stage at 12 months after phase II cardiac rehabilitation completion.

	Under 30 in BMI OR (95% CI)	≥ 150 min of physical activity OR (95% CI)	HADS - Anxiety score below 8 OR (95% CI)	HADS - Depression score below 8 OR (95% CI)
Age (years)	1.0 (1.0–1.0)	0.9 (0.9–0.9)	1.0 (1.0–1.0)	not sign
Gender (Female)	0.7 (0.6–0.8)	not sign.	not sign	not sign
Employment Status (Unemployed)	not sign.	not sign.	1.4 (1.2–1.8)	1.4 (1.1–1.8)
Marital Status (Partnered)	not sign.	1.1 (1.0–1.3)	not sign	not sign
Post CR status				
Never in the optimal stage	Reference	Reference	Reference	Reference
Improved upon completion	14.6 (11.1–19.2)	2.6 (2.3–3.0)	3.3 (2.6–4.1)	3.3 (2.6–4.3)
Always in the optimal stage	134.0 (112.4–159.8)	8.7 (7.6–10.0)	16.6 (14.0–19.6)	21.0 (17.0–25.8)
Comorbidities				
No Comorbidities	Reference	Reference	Reference	Reference
One to Two comorbidities	0.6 (0.5–0.8)	not sign.	not sign	not sign
Three or more comorbidities	0.4 (0.3–0.6)	0.7 (0.6–0.8)	0.8 (0.6–0.9)	0.7 (0.6–0.9)
Cardiovascular Treatment				
No Cardiac Treatment	Reference	Reference	Reference	Reference
PCI	1.4 (1.2–1.7)	not sign.	not sign	not sign
CABG	not sign.	1.4 (1.2–1.7)	not sign	not sign
Other Treatment	not sign.	not sign.	not sign	not sign

Abbreviations: BMI: Body mass index, HADS: Hospital Anxiety and Depression Scale, OR: Odds ratio, CI: Confidence interval, CABG: Coronary Artery Bypass Graft, not sign: Not Significant and omitted in backwards model, PCI: Percutaneous Coronary Intervention.

services is possible – knowledge sought for by the European Association of Preventive Cardiology [3].

**5. Limitations**

The long-term assessment at 12 months is not performed systematically by all programmes in the UK. Despite this, we identified 32 programmes with sufficient size conducting 12-month assessments. However, only a small sample were eligible (47%). Thus, caution should be taken in interpreting the results widely as they may not be generalisable to the entire cardiac population. In addition, only 18% of the NACR database programmes had a well-established mechanism and methodology to collect the 12-month assessment. The results may, therefore, be based on data for high performing programmes [41].

We used clearly defined optimal stages as benchmarks for health and risk factor in people with cardiac conditions. The disadvantage is that some information of within group changes above or below a certain optimal stage was not accounted for in our analysis. CR targets other risk factors than those available in the NACR data, e.g. lipids profile and blood pressure [3]. Therefore, further investigations with other risk factors are needed before a conclusion can be made concerning other risk factors than the four risk factors present in this study.

Another limitation of this study is that service-level factors, known to influence CR provision [42], were not included. As this information is not available for many patients, we were unable to include such factors in our regression models. Finally, we were unable to collect data on CR-adherence to address if our finding related to the fact that adherent patients also were more likely to be adherent at 12 months.

**6. Conclusion**

Using routine CR service data, we found large variation across patient characteristics in the provision of long-term service assessments in the UK. Patients undergoing invasive treatment procedures or having comorbidities were more likely to be assessed at 12 months. However, patients from highly deprived areas were less likely to be assessed. Being in an optimal stage upon CR completion for the four common cardiovascular risk factors was also associated with attending the 12-month assessment. Moreover, this variable was the only one consistently associated with maintaining a positive long-term risk factor status. Thus, the conclusions of this work are that being in an optimal stage upon routine CR completion should be an important assessment and predictor in the provision of a long-term CR service. Additional work should seek

**Table 4**

The actual distributions of patients and estimated margins distributing the percentages of patients in the three optimal risk factor stages for each of the four outcomes at 12 months.

BMI	Total		Always in optimal stage	Improved throughout completion	Not in optimal stage upon completion
	Count	Percent	Estimated percentages	Estimated percentages	Estimated percentages
Over 30					
in BMI	4.244	26,7%	4,1%	27,2%	83,2%
Under 30					
in BMI	11.664	73,3%	95,9%	72,8%	16,8%
Total	15.908	100%	–	–	–
Physical Activity for 150 min					
No	3.983	23,6%	7,8%	21,8%	41,9%
Yes	12.864	76,4%	92,2%	78,2%	58,1%
Total	16.847	100%	–	–	–
HADS Anxiety score					
≥8	3.558	23,0%	4,6%	23,3%	50,0%
<8	11.906	77,0%	95,4%	76,7%	50,0%
Total	15.464	100%	–	–	–
HADS Depression score					
≥8	2.268	14,7%	7,3%	27,9%	56,2%
<8	13.190	85,3%	92,7%	72,1%	43,8%
Total	15.458	100%	–	–	–

Abbreviations: BMI: Body mass index, HADS: Hospital Anxiety and Depression Scale.

to validate these findings taken other patient- and service-related factors into consideration.

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### CRedit authorship contribution statement

**Lars Hermann Tang:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Visualization. **Patrick Doherty:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing. **Søren T. Skou:** Conceptualization, Methodology, Validation, Writing – review & editing. **Alexander Harrison:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft.

### Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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