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Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women: results from the SWEDEHEART registry

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Aims
Participation in exercise-based cardiac rehabilitation (exCR) increases aerobic capacity and improves outcomes in patients following myocardial infarction (MI) and is therefore universally recommended. While meta-analyses consistently report that participation in exCR reduces cardiovascular mortality, there are conflicting results regarding effects on total mortality. Presently, many eligible patients do not receive exCR in clinical practice. We aimed to investigate the relation between participation in exCR post-MI and total mortality in men and women in a nationwide real-world cohort from the SWEDEHEART registry.

Design
Longitudinal, observational cohort study.

Methods and results
In total, 20,895 patients from the SWEDEHEART registry were included. Mortality data were obtained from the Swedish National Population Registry. During a mean of 4.55 (±2.33) years of follow-up, 1000 patients died. Using Cox regression for proportional odds and taking a wide range of potential confounders into consideration, participation in exCR was related to significantly lower total mortality [hazard ratio (HR) 0.72, 95% confidence interval 0.62–0.83]. Excluding patients with shorter follow-up than 2 years did not alter the results. Exercise-based CR participation was related to lowered total mortality in most of the investigated subgroups. The risk reduction was more pronounced in women than in men (HR 0.54 vs. 0.81, respectively).

Conclusion
Participation in exCR was associated with reduced total mortality, and more pronounced in women, compared with men. Our results further support the recommendations to participate in exCR, and hence we argue that exCR should be a mandatory part of comprehensive CR programmes, offered to all patients post-MI.

Keywords
Myocardial infarction • Gender • Mortality exercise • Cardiac rehabilitation • Registry
Introduction

Acute and chronic cardiovascular disease (CVD) including acute myocardial infarction (MI), causes a large proportion of all disability and death worldwide, placing a substantial burden on the healthcare systems. There are several well-known risk factors for CVD, including increasing age, male sex, and unhealthy lifestyle habits. During the last decades, an increased number of individuals survive the acute phase of MI, leading to more patients being in need of secondary prevention.

It is recommended that secondary prevention should be provided through comprehensive cardiac rehabilitation (CR) programmes, which includes several core components, e.g. smoking cessation, physical activity as well as nutritional counselling, psychosocial management, and exercise training, generally referred to as exercise-based CR (exCR). Participation in exCR after an MI is given a class 1A recommendation by the European Society of Cardiology. A key component of exCR is an individually prescribed supervised, centre-based, exercise programme, including progressive aerobic and muscle resistance exercise, aimed to improve aerobic capacity, muscle mass, cardiometabolic risk factors, and psychological well-being.

The latest Cochrane meta-analysis on exCR from Anderson et al. showed that participation in exCR post-MI resulted in a 26% relative risk reduction of CVD mortality. However, while both Anderson et al. and previous Cochrane reports have clearly demonstrated the beneficial effects of exCR on CVD mortality, there has long been uncertainties regarding effects on total mortality. However, in a systematic review (the CROS-II, an update of previous efforts), Salzwedel et al. showed lowered mortality following participation in comprehensive CR, with supervised and structured exercise as a prerequisite for inclusion. While this is of great importance, there is a need to evaluate the isolated benefits of exCR. Also, despite beneficial effects, the current underuse of exCR is a matter of concern and new data could aid the implementation of exCR.

Importantly, gender differences have not been specifically addressed in previous studies on exCR. Even though more recent randomized controlled trials have included more women and older patients, study populations still consist predominantly of lower risk middle-aged men. Since exCR may affect men and women differently, this is unfortunate and highlights a need for gender-stratified studies more representative of real-life clinical practice.

Therefore, the aim of this study was to assess the association between participation in exCR and total mortality in a large unselected nationwide cohort of patients post-MI, including gender specific analyses.

Methods

Data were obtained from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). SWEDEHEART is a nationwide quality registry providing continuous information on acute care and secondary prevention for patients with MI in Sweden. Information on the acute care has a centre-based uptake of 100% and an individual-level uptake of >90%. The individual-level coverage for secondary prevention variables is >75%, making this cohort highly representative of the Swedish patients with MI. The validity of the SWEDEHEART registry data is considered high. On a yearly basis, comparisons made between medical records data and SWEDEHEART registry data are in >95% agreement.

For this study, from the acute phase, data on admitting centre/hospital, age, gender, body mass, height, date and type of MI, diabetes, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), and percutaneous coronary interventions (PCI) were used. Individuals between 18 and 74 years were included in this study. Body mass index (BMI) was subsequently calculated (kg/m²). Before analyses, both age and BMI were dichotomized into two groups by using the median A diagnosis of diabetes (previous or new-onset), which was coded as yes or no. Estimated glomerular filtration rate was based on serum creatinine values (sCr) calculated according to the Cockcroft–Gault formula \( \text{eGFR} = (1.23 \times (140 - \text{age}) \times \text{body mass}/\text{serum creatinine} \) and \( \text{eGFR} = (1.04 \times (140 - \text{age}) \times \text{body mass}/\text{serum creatinine} \), for men and women, respectively, which has previously been used in analyses of SWEDEHEART registry data. Before analyses, the cut of was set to 60 mL/min/1.73 m², separating normal or mildly decreased GFR from moderately decreased or more pronouncedly decreased GFR. Left ventricular ejection fraction expressed in percent and was further divided into <40%, 40–50%, or >50%. Treatment with PCI during hospital care was coded as yes or no. Type of MI was based on a clinical assessment and patients were classified as having had a ST-elevation MI (STEMI), or a non-ST-elevation MI (non-STEMI).

Secondary preventive follow-up data from SWEDEHEART is collected at two follow-up visits, at 6–10 weeks and 12–14 months post-MI. Regarding covariates, we selected the variables existing in the SWEDEHEART registry which we a priori considered being of most importance and had been used in similar studies (for comparison reasons).

Included covariates were health-related quality of life (HRQoL), attending interactive group patient education (so-called Heart School), pharmacological treatment, physical activity level, and smoking status. The included covariates were all collected at the first follow-up visit (6–10 weeks post-MI). To estimate HRQoL, the Euro-Qol 5 dimensions (EQ-5D)-3L scale was used. The EQ5D values were converted into a single summary index, ranging from −0.594 to 1, where 1 represents the best possible health. In analyses, the median of the EQ-5D-values was used to dichotomize the study population in low and high HRQoL. The Heart School is generally defined as basic education in brief lecture format led by specialists on CVD, diet, exercise, and smoking. Each hospital arranges the Heart School as local group sessions led by a cardiologist, cardiac nurse, physiotherapist, dietitian, and/or psychologist. Each session has a disease-specific educational purpose, predominantly delivered as an initial theoretical lecture followed by an open-group discussion for ~1 h each. At some hospitals, the Heart School involves repeated sessions held once per week while at others, half or whole-day sessions are organized. The representation of cardiologists and allied professionals leading the Heart School varies to some extent across hospitals, dependent on professional representation. Additionally, health-promoting interaction in the group setting between patients with MI is a core component.

Data on participation in Heart School were classified as yes or no.

Full pharmacological secondary prevention treatment was identified as being treated with ACE-inhibitors, beta-blocking agents, statins or other lipid-lowering agents, and anti-platelet agents, coded as yes or no.

Physical activity level was self-reported as the number of days during the last week where a session of moderate intensity physical activity, 30 min or longer, was performed. Low physical activity was defined as 0–1 session per week. Moderate activity was defined as 2–4 sessions per week and high 5–7 sessions per week, as previously described. Smoking
status was self-reported and grouped as never-smoker, ex-smoker (since more than 1 month), or current smoker.

The exposure variable, participating in exCR, was obtained at the second follow-up visit. In SWEDHEART, participation in exCR is defined as participation in centre-based supervised exercise sessions, at least two sessions/week. According to the registry, data were coded as non-participating, participating <3 months and participating more or equal to 3 months. In order to create appropriately large groups with sufficiently number of case fatalities in the analyses, the variable was coded as participating in exCR regardless of total programme duration, yes or no.

The primary outcome, total mortality was obtained via merging with the Swedish National Population Registry. The Swedish National Population Registry is managed by the national agency Statistics Sweden (SCB) and is consecutively updated. The registry has an extensive coverage of the total Swedish. Mortality and date of death data are highly consistent with the Swedish cause of death registry. For this study, data were extracted on 7 October 2014.

The study population consisted of patients between ages 18 and 75 years who were diagnosed with their first MI (ICD-code I21) between 28 December 2004 and 25 October 2013. In addition, complete data on covariates, explanatory, and outcome variables (as outlined above) were required for inclusion. The Regional Ethics Board in Stockholm, Sweden approved this study (registration number: 2013/2067-31) which complies with the Declaration of Helsinki.

Descriptive demographic and clinical characteristics were analysed using frequencies and relative frequencies. Differences between included vs. non-included patients as well as between survivors vs. fatal cases and the exCR vs. non-exCR strata were tested using the χ² test. For the χ² tests, we applied a Benjamini–Hochberg correction to adjust for multiple comparisons.

Time to event was studied using two Cox-proportional hazard regression models in the two exCR-strata. The first model was age and gender adjusted and the second was a fully adjusted model, including admitting centre/hospital, age, BMI, date for admission, diabetes, eGFR, gender, HRQoL, LV function, type of MI, PCI, pharmacological treatment, physical activity level participation in heart school, and smoking habits. Prior to the Cox regressions, the proportionality assumption was checked using the Schoenfeld residuals, finding no sign of violation. Firstly, gender-stratified analysis was performed, adjusting for the same covariates as above. In subsequent post-hoc analyses, to study differences in the association between exCR participation and mortality by different covariates, further stratified Cox regressions were done.

The Cox regressions were performed by formal interaction analyses using interaction term in the model. Hazard ratios (HRs) were considered to be statistically significant if the 95% confidence interval (CI) did not include the value of 1. All statistics were performed in Statistical Package for the Social Sciences (SPSS) 21.0 (IBM Corp., Armonk, NY, USA).

Results

Of the total 48 718 patients with survival data, 20 895 presented a full set of data (Figure 1). The study population consisted of 74% men with a median age of 63 [interquartile range (IQR) 12] years, 43% had a STEMI and 60% had an LVEF of ≥50%. Moreover, the median BMI was 26.9 (IQR 5.1) kg/m², 13% had a diabetes diagnosis (previous or new-onset), and the median of EQ5D was 0.85 (IQR 0.28). A total of 9647 (46%) patients participated in exCR. Of those, 7942 patients participated <3 months and 1705 patients participated for ≥3 months.

Compared to patients who lacked one or more variables (non-included), the included patients were younger, more likely to be male, non-smokers, have participated in exCR and Heart School, have STEMI, having undergone PCI, receive full medication, and fewer were diagnosed with diabetes. In addition, included patients had a higher physical activity level, eGFR, HRQoL, and a lower BMI. All these differences were small, albeit statistically significant (P < 0.05, see Supplementary material online 1).

When comparing all individuals participating in exCR to non-participants, the groups differed slightly, however, significantly (P < 0.05). Participants in exCR were younger, more likely women (27% vs. 25%), non-smokers, non-diabetics, have had STEMI, received full medication, and participated in Heart School. Moreover, they had a higher physical activity level, eGFR, and HRQoL. However, BMI, LVEF, and having undergone PCI did not relate to exCR attendance (Table 1).

Mean follow-up time (i.e. between date for MI and date of death or end of study) was 4.55 (SD 2.33) years. During follow-up, a total of 1000 fatal cases were observed. In the total study population, the mortality was 10.52 cases per 1000 person-years. The unadjusted mortality varied across exCR strata, with 13.48 cases per 1000 person-years among non-participants and 7.06 cases per 1000 person-years among participants.

Compared to non-participation and controlling for age and gender, HR for mortality (95% CI) for patients participating in exCR was 0.55 (95% CI: 0.48–0.63). In the fully adjusted analyses, the decreased mortality-risk remained for participants, with HR 0.72 (95% CI: 0.62–0.83) compared to non-participants (Figure 2).

To take the possible effect of early mortality into account, we excluded patients (n = 3217) who died or were lost to follow-up within 2 years of the acute event. Based on the remaining 17 678 patients and 857 fatal cases, results were similar to those in the full sample (HR for participation in exCR was 0.70, 95% CI: 0.60–0.82).

To study differences in relations between exCR and mortality between genders, a formal interaction analysis was performed. Results revealed significant interaction effects of exCR, showing that women participating in exCR had significantly lower HR, compared to men participating in exCR.

The relation between exCR participation and mortality stratified by the factors in the full model was further analysed and presented in Table 2. Participation in exCR was related to lower mortality in most investigated subgroups. Formal interaction analysis revealed significant interaction effects of exCR between HRQoL strata, with EQ5D-score below median being related to significantly lower HR, compared to above median.

Discussion

To the best of our knowledge, this is the first time total mortality benefits related to participation in exCR have been shown from exCR over time in a large, unsel ected nationwide cohort of patients with MI. Results remained after adjusting for several potential confounders and early mortality (within 2 years of the acute event). This is in line with a few earlier studies reporting reduced total mortality.
following an exercise intervention as part of a comprehensive CR programme. However, there are conflicting results, as the Cochrane report by Anderson et al. showed an association between exCR attendance and decreased CVD mortality, but not total mortality. Therefore, the results of the present study, showing decreased total mortality in exCR participants, is of great clinical importance, further supporting efforts to increase referral, attendance, and adherence to exCR programmes.

Importantly, this large cohort also enabled gender-stratified analyses. Previous exCR-studies have often included more men and individuals with less severe disease, making sub-group analyses difficult. The strength of the association between exCR participation and mortality was more pronounced in women than in men. One contributing factor for the gender difference is a higher treatment potential in women, as women have a higher lethality, compared to men. In further post-hoc analyses, the results across investigated strata, including age, BMI, diabetes, eGFR, LVEF, type of MI, PCI, pharmacological treatment, physical activity level, and smoking habits were similar, consistently showed an association between exCR participation and lower mortality. One exception was patients with low HRQoL, who had lower HR for total mortality of exCR, compared to patients with a high HRQoL.

Earlier and recent publications have identified a general reduction of all-cause mortality for participating in cardiac rehabilitation that includes, but not restricted to, structured and supervised exercise. This article present novel findings on the gender difference in the relation between exCR participation and mortality which is important, since there is a lack of studies that have been able to compare this relation, especially in unselected cohorts. Another interesting observation in our study was that women were found to be overrepresented among exCR participants, which is only partially in line with earlier research. Internationally, lower referral rates to exCR programmes among women compared to men is a well-described problem.

In line with the current results, recently published Swedish data showed that female sex was indeed associated with higher exCR attendance. Previous studies identify different gender-related barriers. Witvrouw en et al. listed gender differences in both physiological responses to exCR and psychological barriers for participation. Their narrative review identified both time available for exercise and psychological factors to be important factors, suggesting the need for gender-tailored exCR. This is consistent with the results from Resurreccion et al. considering family obligations and caretaking responsibilities as barriers for participation in exCR among women. The fact that Sweden is one of the most gender-equal countries in the world may explain this contradictory finding. However, as our results suggest women to have greater benefit of attending...
ExCR compared to men, high referral and participation rates among women are important to maintain. Further, we found a significant difference in HRs between strata of HRQoL, indicating that exCR may be even more important in groups with a low HRQoL. This underlines the importance of structural evaluation of psycho-social health aspects in the referral process to exCR. Lastly, the finding that the effect of exCR on mortality between subgroups with different levels of disease severity (e.g., LV function, eGFR, type of MI, diabetes) did not differ is clinically important, since individuals with more severe disease are less likely to be included in exCR programmes, although having the same potential benefits. Unfortunately, effective strategies on increasing inclusion into exCR are scarce. Therefore, efforts are needed to identify effective ways to promote and provide equal access to exCR for all patients.

Previous research has mainly been based on experimental design, mostly randomized controlled clinical trials (RCTs). Although RCTs have many advantages, many of the existing meta-analyses indicate high or unclear risk of bias regarding blinding, attrition, and selection, reducing the internal validity. Randomized controlled clinical trials also have the inherent risk of over-representing low-risk patients. A strength with this study is that the SWEDEHEART registry collects data from almost all patients with an index event of acute MI in Sweden and, as such, represents a unique, unselected real-world cohort of patients with MI, both in terms of heterogeneity and national representability. The study design supports a better understanding of the natural course of lifestyle and its changes over time, compared to experimental studies, which increases the generalizability of the results.

| Table 1 | Baseline characteristics by non-participants and participants in exercise-based cardiac rehabilitation |
|---------|---------------------------------------------------------------|
|          | No ExCR | ExCR |
| N        | 11 248  | 9647 |
| Age (median) |         |      |
| <63 years | 5639* (50.1%) | 5326* (55.2%)* |
| ≥63 years | 5609* (49.9%) | 4321* (44.8%) |
| BMI (median) |         |      |
| <26.9 kg/m² | 5679* (50.5%) | 4744* (49.2%) |
| ≥26.9 kg/m² | 5569* (49.5%) | 4903* (50.8%) |
| Diabetes |         |      |
| No | 9651* (85.8%) | 8582* (89.0%)* |
| Yes | 1597* (14.2%) | 1065* (11.0%) |
| eGFR |         |      |
| Decreased (<60 mL/min/1.73 m²) | 1021* (9.1%) | 612* (6.3%) |
| Normal (≥60 mL/min/1.73 m²) | 10 227* (90.9%) | 9035* (93.7%) |
| Full medication |         |      |
| No | 3512* (31.2%) | 2797* (29.0%)* |
| Yes | 7736* (68.8%) | 6850* (71.0%) |
| Gender |         |      |
| Male | 8437* (75%) | 7032* (72.9%) |
| Female | 2811* (25%) | 2615* (27.1%) |
| Heart school |         |      |
| No | 8730* (77.6%) | 4202* (43.6%)* |
| Yes | 2518* (22.4%) | 5445* (56.4%) |
| HRQoL (EQ5D, median) |         |      |
| <0.85 | 4836* (43.0%) | 3898* (40.4%)* |
| >0.85 | 6412* (57.0%) | 5749* (59.6%) |
| LVEF |         |      |
| <40% | 1515* (13.5%) | 1202* (12.5%) |
| 40–49% | 2299* (20.4%) | 1937* (20.1%) |
| ≥50% | 7434* (66.1%) | 6508* (67.5%) |
| Physical activity sessions/week |         |      |
| 0–1 | 2716* (24.1%) | 1277* (13.2%)* |
| 2–4 | 3071* (27.3%) | 2895* (30.0%) |
| 5–7 | 5461* (48.6%) | 5475* (56.8%) |
| PCI during hospital stay |         |      |
| No | 2293* (20.4%) | 1884* (19.3%) |
| Yes | 8955* (79.6%) | 7763* (80.5%) |
| Smoking |         |      |
| Never smoker | 3410* (30.3%) | 3437* (35.6%)* |
| Ex-smoker | 6346* (56.4%) | 5448* (56.5%) |
| Current smoker | 1492* (13.3%) | 762* (7.9%) |
| STEMI |         |      |
| No | 6524* (58.0%) | 5327* (55.2%)* |
| Yes | 4724* (42.0%) | 4320* (44.8%) |

Testing of differences between exCR strata was based on two-sided tests.

* A significant difference, as P < 0.05. Significances were adjusted using Benjamini–Hochberg correction where appropriate.

a, b Each subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at p<0.05.
Limitations to the study

On the other hand, there are limitations in using registry-based data. Being an observational study, a cause-effect relationship cannot be confirmed. As several variables are self-reported, including participation in exCR, data validity can be affected. In addition, details about dose and duration of the exercise programmes provided within exCR were not registered. Also, patients may have participated in other components included in a comprehensive CR programme, e.g. smoking cessation programmes and diet counselling. The relative effect from different parts of the intervention in this study is unknown.

In order to be included in the study population, patients had to have complete data of covariates, explanatory and outcome variables, thereby excluding a high number of individuals, leading to a risk of selection bias. However, the association between exCR and mortality seem to be similar across subgroups. Another limitation is the age limit in the SWEDHEART registry of <75 years at the time of the study, which limits the generalizability of our results to older patient populations. The lack of cause-specific mortality is a limitation, preventing more detailed analysis of any difference in cause of death between exCR-strata and gender. The lack of information on the nature of the events causing mortality after CR also limits the present study’s ability to separate cardiovascular and non-cardiovascular causes and to conclude that CR reduces cardiovascular mortality specifically. In this study, the use of the generic HRQoL used in this analyses, could be substituted to disease-specific instrument for higher resolution and possible higher validity. In future studies, CVD-specific mortality, major cardiovascular events, and diagnosis-specific admissions should be addressed as outcomes.

Noteworthy, this study includes a large cohort with high national coverage allowing multivariate analyses of robust size. Thereto, the registry represents a large variation in risk factors and other covariates. Grant et al. propose a number of considerations regarding the reporting of data in multivariate analyses. Most of these have been met, as described above. In addition to these, we state that univariate analyses only were performed for mortality, not time to event.

The results that participation in exCR is associated with reduced total mortality, in both men and women, in a nationwide, unselected cohort study, is of great clinical importance, and adds to the current knowledge in the field. The findings also draw attention to the underuse of exCR in clinical practice, and could aid in highlighting the work to further implement exCR for individuals post-MI.

In conclusion, the present study, based on a nationwide cohort of Swedish patients with MI, demonstrated a lower total mortality for those participating in exCR compared to those not taking part. Noveau findings include that women seemed to benefit more than men, as did individuals with a low HRQoL compared to individuals with a high HRQoL. This study strongly supports the wider utility of exCR post-MI in clinical practice.

Supplementary material

Supplementary material is available at European Heart Journal – Cardiovascular Pharmacotherapy online.
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**Table 2** Stratified analyses of mortality among non-participants (reference group) and participants in exercise-based cardiac rehabilitation

| Factor                            | Strata            | HR    | 95% CI      |
|-----------------------------------|-------------------|-------|-------------|
| Age (median)                      | <63 years         | 0.77  | 0.60–0.99   |
|                                  | ≥63 years         | 0.70  | 0.58–0.83   |
| BMI (median)                      | <26.9 kg/m²       | 0.69  | 0.56–0.84   |
|                                  | ≥26.9 kg/m²       | 0.75  | 0.61–0.92   |
| Diabetes                          | No                | 0.73  | 0.62–0.85   |
|                                  | Yes               | 0.73  | 0.54–0.99   |
| eGFR                              | Decreased (<60 mL/min/1.73 m²) | 0.55 | 0.39–0.78   |
|                                  | Normal (≥60 mL/min/1.73 m²) | 0.77 | 0.66–0.90   |
| Full medication                   | No                | 0.67  | 0.52–0.87   |
|                                  | Yes               | 0.74  | 0.63–0.88   |
| Gender                            | Male              | 0.81  | 0.68–0.96   |
|                                  | Female            | 0.54  | 0.41–0.72   |
| Heart school                      | No                | 0.67  | 0.56–0.80   |
|                                  | Yes               | 0.86  | 0.66–1.13   |
| HRQoL EQ_5D (median)              | ≤0.85             | 0.63  | 0.51–0.77   |
|                                  | >0.85             | 0.83  | 0.68–1.03   |
| LVEF                              | <40%              | 0.59  | 0.43–0.80   |
|                                  | 40–49%            | 0.79  | 0.59–1.07   |
|                                  | ≥50%              | 0.76  | 0.63–0.93   |
| Number PA sessions/week           | 0–1               | 0.61  | 0.46–0.80   |
|                                  | 2–4               | 0.84  | 0.63–1.12   |
|                                  | 5–7               | 0.75  | 0.61–0.93   |
| PCI during hospital care          | No                | 0.63  | 0.49–0.83   |
|                                  | Yes               | 0.76  | 0.64–0.90   |
| Smoking                           | Never smoker      | 0.87  | 0.67–1.15   |
|                                  | Ex-smoker         | 0.68  | 0.56–0.82   |
|                                  | Current smoker    | 0.68  | 0.45–1.03   |
| STEMI                             | No                | 0.70  | 0.58–0.84   |
|                                  | Yes               | 0.76  | 0.60–0.95   |

Hazard ratios are based on the fully adjusted model.

*Significant interaction between strata as *P* < 0.05.

ExCR is related to reduced total mortality

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