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FULL RESEARCH PAPER
Exercise physiology & testing

Heart rate response and recovery in cycle exercise testing: normal values and association with mortality

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Aims Chronotropic incompetence and impaired heart rate (HR) recovery are related to mortality. Guidelines lack specific reference values for HR recovery. We defined normal values and studied blunted HR response and recovery and mortality risk.

Methods and results We included 9917 subjects (45% females) aged 18–85 years who performed a cycle exercise test. We defined normal values for peak HR, HR reserve, and HR recovery at 1 and 2 min (HRR_1 and HRR_2) based on individuals apparently healthy ($N = 2242$). Associations between blunted HR indices (<5th percentile) and mortality over a median follow-up of 8.6 years were analysed using Cox regression and competing risk analysis. All HR indices were age-dependent and independent predictors of all-cause and cardiovascular (CV) mortality. The 5th percentiles of HR reserve, HRR_1, and HRR_2 correlated weakly with existing reference values. Heart rate recovery variables were the strongest predictors of all-cause mortality in both the overall population [HRR_1, hazard ratio 1.70 (95% confidence interval, 1.49–1.94), and HRR_2, 1.57 (1.37–1.79)] and in subjects with normal exercise capacity [HRR_1, 1.96 (1.61–2.39), and HRR_2, 1.76 (1.46–2.12)]. Combining HR indices appeared to increase the risk of all-cause [HRR_1 and HRR_2, 1.96 (1.68–2.29), and peak HR and HRR_1, 1.87 (1.56–2.23)] and CV mortality, although no specific combination was superior for predicting CV mortality.

Conclusion All HR indices were age-dependent and associated with all-cause and CV mortality. Blunted HR recovery variables were the strongest predictors of all-cause mortality, even in subjects with normal exercise capacity. Combined blunted HR indices appeared to add prognostic value.

Lay summary We provide a detailed description on the physiologic HR response and recovery kinetics in a population apparently CV risk-free and without comorbidities referred for cycle exercise testing. When assessed in a larger population, blunted HR response and recovery were associated with increased mortality.

- Heart rate response and recovery are age-dependent. We provide novel reference values.
- All blunted HR indices (peak HR, HR reserve, HRR_1, and HRR_2) are strong predictors of all-cause and CV mortality, and combined HR indices appeared to add prognostic value in all the analyses.
- Blunted HRR_1 followed by HRR_2 is the strongest predictor of all-cause mortality even in subjects with normal exercise capacity, highlighting the importance of their assessment in standard exercise testing.

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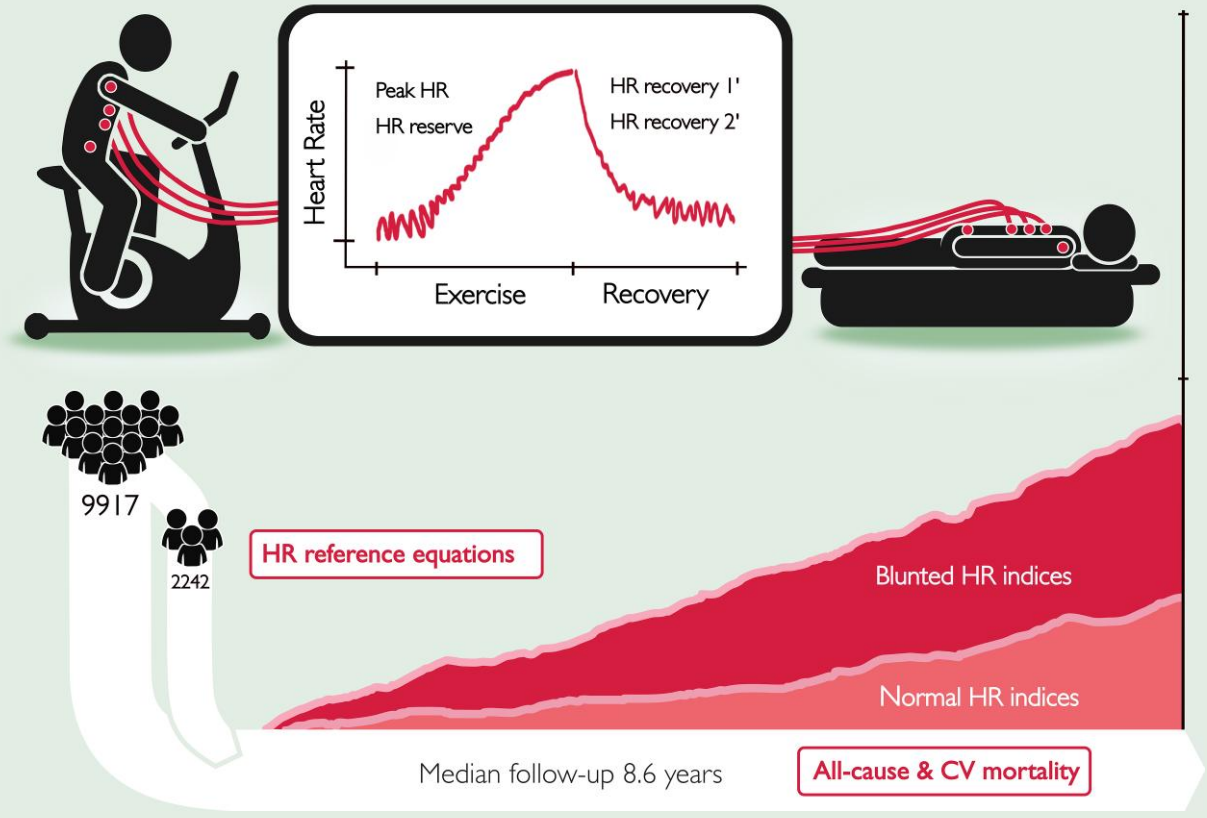
Graphical Abstract



HR, heart rate; CV, cardiovascular.

Keywords Heart rate recovery • Heart rate response • Reference values • Mortality • Cycle exercise test

Introduction

Heart rate (HR) response during exercise, also known as chronotropic response, and HR recovery after exercise are commonly assessed during clinical exercise testing. Chronotropic incompetence is broadly defined as the inability to increase HR proportionally to increased activity or demand and may manifest as delayed increase in HR, blunted peak HR, or HR fluctuations during exercise.[1,2] Heart rate recovery is defined as the deceleration of HR after the cessation of exercise, and impaired HR recovery is described in the literature as a non-invasive marker of autonomic dysfunction.[3,4] Aging, cardiovascular (CV) disease, and deconditioning elicit a shift in autonomic tone towards sympathetic predominance with a decrease in parasympathetic activity, which translates into impaired HR response and HR recovery.[5] The association between HR responses and mortality has been studied extensively, with Ellestad *et al.*[6] suggesting the term chronotropic incompetence, Wilkoff *et al.*[1] proposing the chronotropic index, and Cole *et al.*[7] evaluating the risks related to blunted HR recovery. In individuals referred for exercise treadmill testing, chronotropic incompetence and reduced HR recovery have been found to be independent predictors of all-cause and CV mortality.[7–13]

Guidelines recommend caution when assessing chronotropic incompetence using the traditional 220 – age equation to predict maximal HR, which is prone to large variability across age groups.[4,14] Therefore, other reference values have been proposed,[15] including using the HR reserve rather than only peak HR.[1] The current reference values for HR recovery are fixed thresholds that differ across studies due to differences in exercise (and recovery) protocols and the populations studied. Consequently, there is no universally accepted criterion defining abnormal HR recovery, and current guidelines lack specific recommendations regarding its assessment.[4] The use of cool-down procedures following peak exercise[7] may lead to significantly different HR recovery compared with immediate rest in the supine position.[10] Previous studies have assessed high-risk patients with and without coronary artery disease,[16,17] symptomatic patients with chest pain who had undergone coronary angiography,[11] and patients with heart failure,[13] as well as patients referred for myocardial perfusion imaging.[7,8,10,12,18] Furthermore, most studies are based on treadmill exercise testing, and the prognostic performance of HR response and HR recovery has not been fully examined in subjects undergoing cycle exercise testing.

The aim of this study was to establish normal values for HR response and HR recovery in cycle exercise testing. Additionally, we aimed to investigate whether blunted HR response and HR recovery were related to all-cause and CV mortality in a large age span of the population referred for clinical cycle exercise testing.

Methods

Design and population

This was a longitudinal cohort study of all consecutive individuals aged 18–85 years referred for a cycle exercise stress test at the Department of Clinical Physiology at Kalmar County Hospital between May 2005 and October 2016. The most common reasons for referral were suspected ischaemic heart disease (80%), evaluation of CV performance and exercise capacity (8%), palpitations and arrhythmia evaluation (6%), preoperative assessment (3%), and heart valve pathology or assessment of dyspnoea (3%). This cohort was previously used to establish Swedish reference values for exercise capacity and systolic blood pressure responses.[19–21]

In the present study, two populations were defined. The first group (reference population), consisting of apparently CV healthy individuals without comorbidities, was used to compute reference values and was selected excluding subjects with underlying CV diagnosis and other diseases, CV risk factors, CV medications, and malignant cancer within the last 5 years prior to the exercise test. Individuals were also excluded if they received a diagnosis of ischaemic heart disease, heart failure, and/or atrial fibrillation/flutter or died within 1 year from the exercise test. Lastly, subjects were excluded if they had sinus bradycardia (<40 b.p.m.) or sinus tachycardia (>100 b.p.m.) at rest, extremely high resting systolic blood pressure (>200 mmHg), reduced exercise capacity (<75% of predicted as defined by Brudin *et al.*[19]), arrhythmia during exercise, more than mild chest discomfort (Borg CR10 > 2/10), exercise-induced ischaemia, low systolic blood pressure during maximal effort (<100 mmHg), failure to adequately increase systolic blood pressure during exercise (<40 mmHg increment during the test or a drop in systolic blood pressure), short test duration (<6 min), or if the test was interrupted by the physician for any other reason (*Figure 1A*). The second group (overall population) was used for survival analysis (*Figure 1B*). Subjects in both populations with a submaximal rated perceived exertion (Borg scale < 17), implanted pacemaker, higher HR recovery than peak HR (suggesting sustained arrhythmia post-exercise), and/or a difference between peak HR and HR at the starting time of the recovery phase were also excluded. Additionally, individuals in the overall population who had an accidental (non-medical) death were excluded, and the remaining ones were classified as either CV-related or non-CV–related mortality.

Ethical considerations

The study was approved by the Regional Ethical Review Board (2012/379-31 and 2018/141-31), and individual informed consent was waived due to the use of routinely collected clinical and registry data.

Assessments

Exercise cycle testing data were cross-linked with the Swedish National Patient Register to retrieve all hospital inpatient and outpatient diagnoses, coded with the International Classification of Diseases version 10, the admission diagnoses during the 5 years before and 1 year after the test, and with the National Cause of Death Register to obtain survival status. Medications were documented prior to the test using the Swedish National Prescribed Drug Register. Occurrence of hypertension, diabetes, and hyperlipidaemia was defined based on either a diagnosis or the use of medication for the respective disease.

Subjects were categorized in three different CV risk subgroups before the exercise test. Those with established CV disease had a diagnosis of any of the following: ischaemic heart disease (myocardial infarction, unstable or chronic angina), heart failure, cardiomyopathy, cerebrovascular disease, pulmonary embolism, pulmonary arterial hypertension, peripheral arterial disease, atrial fibrillation/flutter, and/or other arrhythmias. Those with CV risk factors without established CV diagnoses had a diagnosis of diabetes, hyperlipidaemia, hypertension, renal failure, and/or use of CV medication. The remaining subjects were categorized as CV risk-free. A sensitivity analysis was conducted separately for subjects from the overall population with normal exercise capacity and for subjects not using beta-blockers.

Exercise testing

All individuals underwent symptom-limited exercise testing on a cycle ergometer (Rodby Inc., Karlskoga, Sweden) using an individualized ramp protocol with an initial workload between 20 and 100 W followed by a continuous ramp-up with increments of either 10, 15, or 20 W/min. Peak workload was recalculated to a standard protocol with a 10 W/min increment for females and 15 W/min increment for males, to allow comparison between subjects and to assess exercise capacity as described elsewhere.[19] A 12-lead electrocardiogram (ECG) was recorded at rest, before, during, and after exercise (CASE 12; GE Healthcare, Milwaukee, WI, USA). Subjects were encouraged to reach maximal exertion in the absence of any termination criteria: severe chest pain (Borg CR10 ≥ 5), exercise-induced ischaemia (≥4 mm horizontal or downsloping ST depression in ECG lateral leads), decreasing blood pressure, or exercise-induced arrhythmias [ventricular tachycardia defined as at least three premature ventricular contractions (PVCs) in a row, PVCs in increasing frequency or complexity, supraventricular tachycardia > 200/min, or AV block II or III occurring during exercise]. No HR target was used as a criterion for termination of exercise.

Heart rate response

Resting HR was recorded in the supine position after a few minutes of rest. Heart rate response was continuously monitored during exercise, and HR at 25, 50, 75, and 100% of achieved peak workload was computed. Chronotropic incompetence has commonly been defined with the threshold < 85% of maximal HR or <80% HR reserve (both using age-predicted maximal HR based on the 220 − age equation). Peak HR was defined as the maximal HR achieved during peak workload. Heart rate reserve was defined as the difference between peak HR and resting HR, and the percentage of HR reserve was calculated as 100 × ([peak HR − resting HR]/[age-predicted maximal HR − resting HR]). Lower limit of normal (LLN) for peak HR and HR reserve was defined separately for males and females using the lower 5th percentile in the reference population.

Heart rate recovery

There was no cool-down period after achieving peak workload, and all subjects went into a supine position as soon as possible post-exercise. Heart rate recovery was defined as the difference between peak HR and the HR at a specific time after cessation of exercise. Heart rate recovery at 1, 2, 3, and 4 min (HRR_1, HRR_2, HRR_3, and HRR_4) was registered, although only HRR_1 and HRR_2 were further investigated. Lower limit of normal for HRR_1 and HRR_2 was defined separately for males and females using the 5th percentile the reference population. LLN HRR_1 and LLN HRR_2 were compared with the most commonly used reference values for HR recovery at 1 and 2 min.[7,10–12]

Endpoints

Participants were followed prospectively for the primary endpoints of all-cause and CV mortality using the mandatory Swedish National Cause of Death Registry.

Statistical analyses

All analyses were performed using R 4.2 (R core team, 2023). Specifically, the packages used for Cox regression analysis and competing risks were 'cmprks::crr' (sub-distribution hazard model) and 'survival::coxphs' (cause-specific hazard model). Means were compared using Student's *t*-test and proportions using the χ^2 test. We analysed means of more than two groups with one-way ANOVA and the Bonferroni post-hoc test. A $P < 0.05$ was considered statistically significant. Pearson correlation coefficients were categorized as follows: 0–0.19 as negligible, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong, and 0.80–1 as very strong correlation.[22]

Sex-specific quantile regression equations with 5th and 50th percentiles were determined for peak HR and HR reserve, and unisex equations were determined for HRR_1 and HRR_2. Previously reported independent variables

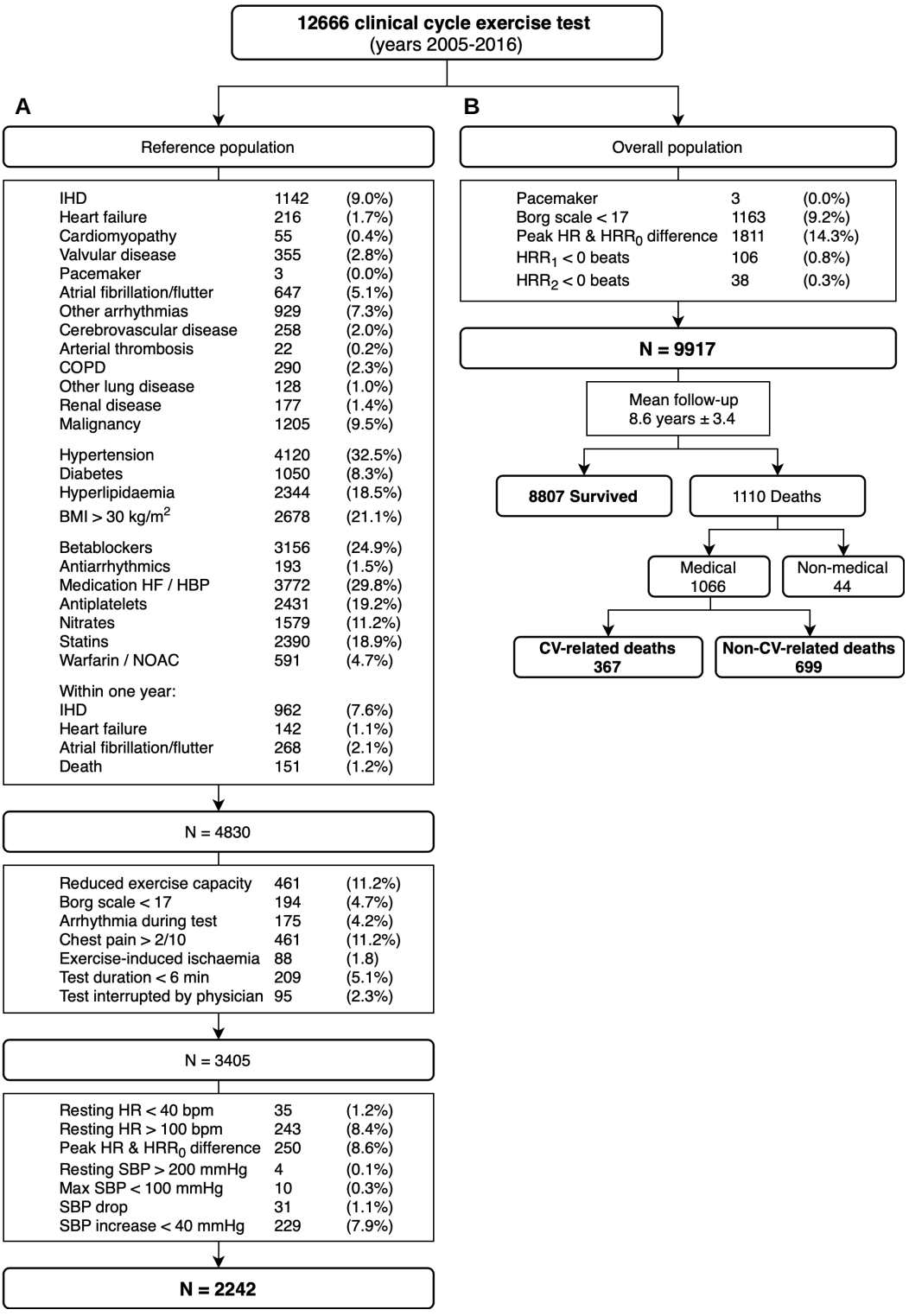


Figure 1 Selection of final samples: (*A*) selection of reference population and (*B*) selection of overall population and follow-up. Subjects could have more than one exclusion criterion. IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Medication HF/HBP, medication for heart failure or hypertension, not including beta-blockers; NOAC, non-warfarin oral anticoagulant; SBP, systolic blood pressure; HR, heart rate; HRR_0, heart rate recovery at minute 0; HRR_1, heart rate recovery at minute 1; HRR_2, heart rate recovery at minute 2.

from the literature (age, age squared, resting HR, and BMI) were evaluated and used in the stepwise backward variable selection algorithms to achieve the best Akaike information criterion, although our model selection process was also guided by the principle of parsimony, aiming for a balance between model complexity and explanatory power. Age squared, BMI, and resting HR were significant predictors of peak HR and HR reserve for males and females, suggesting some nonlinear effect of age on HR response. The model for HRR_1 included age, age squared, and resting HR, while the model for HRR_2 included age, age squared, resting HR, and BMI, indicating both linear and nonlinear effects of age on HR recovery. Subjects in the overall population were divided into two subgroups based on the LLN (5th percentile of the reference population) for each HR response and HR recovery variable. Because resting HR was included into the peak HR predicting model, it yielded a perfect correlation with HR reserve. Thus, further survival analysis for HR response in the overall population utilized only peak HR and LLN peak HR. Subjects were stratified into four age groups for comparison: 18–40, 41–50, 51–60, and 61–85 years.

Follow-up time was calculated for each subject from the date of the test to the date of death or 30 April 2019, whichever came first. For survival analysis, Kaplan–Meier curves were plotted. Cox proportional hazard ratios with 95% confidence intervals were calculated for peak HR (implicitly reflecting HR reserve), HRR_1, and HRR_2, and their combinations for all-cause and CV mortality. To study the combined effects of different HR variables and avoid collinearity, we created new categorical variables for the different variable pairs (HRR_1 and HRR_2; peak HR and HRR_1; and peak HR and HRR_2) with four different categories (both indices normal, first blunted, second blunted, or both blunted). Competing risk analysis was performed using both subdistribution hazard analysis and case-specific hazard analysis. Three mortality risk prediction models were used: model 1: unadjusted; model 2: adjusted for age, sex, and BMI; and model 3: adjusted for age, sex, BMI, exercise capacity, resting HR, CV risk category at baseline, and use of beta-blockers. To evaluate the consistency of the Cox regression and competing risk analysis, a comprehensive bootstrapping analysis was performed.

Results

Reference population

A total of 2242 subjects (38% female), considered CV risk-free and without comorbidities, were included in the reference population, with a mean age of 49 years ± 14. Their characteristics and cycle exercise test data are presented in Supplementary material online, *Table S1*. Mean peak rated perceived exertion (Borg scale) of 17.6 and an exercise capacity close to 100% of the expected was achieved for males and females.[19]

Peak HR, HR reserve, HRR_1, and HRR_2 decreased with age in a nonlinear fashion for males and females (*Figure 2*). Sex-specific quantile regression equations were computed for peak HR and HR reserve using age squared as the main independent variable in the prediction equations (*Table 1*). As shown in *Figure 2*, there was a negligible difference in HR recovery between males and females. Consequently, unisex quantile regression equations for HRR_1 and HRR_2 were preferred and used for survival analysis (*Table 1*). In the Supplementary material, an Excel file is available for calculating normal values using the quantile regression equations, including a simplified version based solely on age-related variables (age and age^2).

Peak HR for males and females (50th percentile values based on our own equations) was compared with the 220 – age equation and Tanaka's equation (208 – 0.7 * age).[15] The 220 – age equation overestimated maximal HR in young individuals and Tanaka's equation had higher maximal HR for all ages, overestimating maximal HR in older individuals the most (*Figure 2A*). However, in a simplified model (50th percentile quantile regression) where only age was used as predictor, peak HR was almost equal to the prediction from Tanaka's equation for males (207 – 0.8 * age), though lower for females (199 – 0.7 * age). On the other hand, there was a very strong correlation between 85% age-predicted maximal HR (based on the 220 – age equation) and LLN peak HR ($r = 0.90$, $P < 0.01$), as displayed in Supplementary material online, *Figure S1A*. LLN HR reserve was compared with 80% of HR reserve, revealing a negligible correlation ($r = 0.21$, $P < 0.01$), as it had a decreasing trend from under 80% in young subjects to under 60% in older subjects for males and females (see Supplementary material online, *Figure S1B*).

HRR_1 and HRR_2 quantile regression equations based on our findings were compared with the most commonly used reference values for HR recovery in the literature (*Figure 2C and D*). LLN HRR_1 in subjects over 65 years was lower than the previously suggested threshold of 18 b.p.m. and decreased under 12 b.p.m. in subjects above 75 years (*Figure 2C*). LLN HRR_2 in subjects above 55 years was lower than the threshold of 42 b.p.m. and was above the threshold of 22 b.p.m. for all subjects (*Figure 2D*). There was a strong correlation between HRR_1 and HRR_2 ($r = 0.78$, $P < 0.001$).

Chronotropic response exhibited a trend of progressively slightly steeper HR increase as the metabolic demand augmented (increase in workload), as observed in Supplementary material online, *Figure S2A and C*. On average, a higher peak HR was measured in males, although the difference in HR peak between sexes decreased with age.

Heart rate recovery exhibited a trend of decreasing HR, with the fastest decrease occurring during the first minute post-exercise (HRR_1). After that, HR recovery continued to decrease at a slower rate until the last recording at 4 min post-exercise. This trend is illustrated in Supplementary material online, *Figure S2B and D*. There was a negligible correlation between percentage of predicted exercise capacity and HRR_1 ($r = 0.07$, $P < 0.001$) and a weak correlation between peak HR and HRR_1 ($r = 0.30$, $P < 0.001$).

Survival analysis

A total of 9917 subjects (aged 58 ± 14.6 years, 45% females) were included in the survival analysis with a median of 8.6 (5.9–11.6) years of follow-up corresponding a total person-year follow-up of 85 631 (*Figure 1B*). A total of 1100 deaths occurred during follow-up (11%), of which 44 were accidental deaths (4%) and 367 were CV deaths (33%). At the time of the test, 4628 (47%) appeared CV risk-free, 3629 (36%) had one or more CV risk factor but no established CV disease, and 1660 (17%) had a diagnosis of CV disease. On average, all haemodynamic parameters, HR response, and HR recovery, as well as exercise capacity, were lower in the subgroup with non-CV mortality, but lowest in the CV mortality subgroup compared with the surviving group (*Table 2*). Furthermore, HR response and HR recovery inversely correlated with the number of major CV risk factors (hypertension, hyperlipidaemia, diabetes, and BMI over 25) as shown in Supplementary material online, *Figure S3*. Overall population characteristics and standard exercise test data by sex are presented in Supplementary material online, *Table S2*.

Kaplan–Meier survival analysis for peak HR, HRR_1, and HRR_2 for all-cause mortality displayed lower mortality rates at a median of 8.6 years of follow-up in subjects with normal HR indices (*Figure 3*). Furthermore, we analysed peak HR, HRR_1, and HRR_2 in combination with normal or reduced exercise capacity, revealing similar mortality rates in subjects with normal exercise capacity and blunted HR recovery, compared with those with reduced exercise capacity and normal HR recovery. Cumulative incidence of CV and non-CV mortality for peak HR, HRR_1, and HRR_2 is presented in Supplementary material online, *Figure S4*.

Blunted peak HR, HRR_1, and HRR_2 significantly increased the risk of all-cause and CV mortality (*Table 3*). No sex interaction effect with any

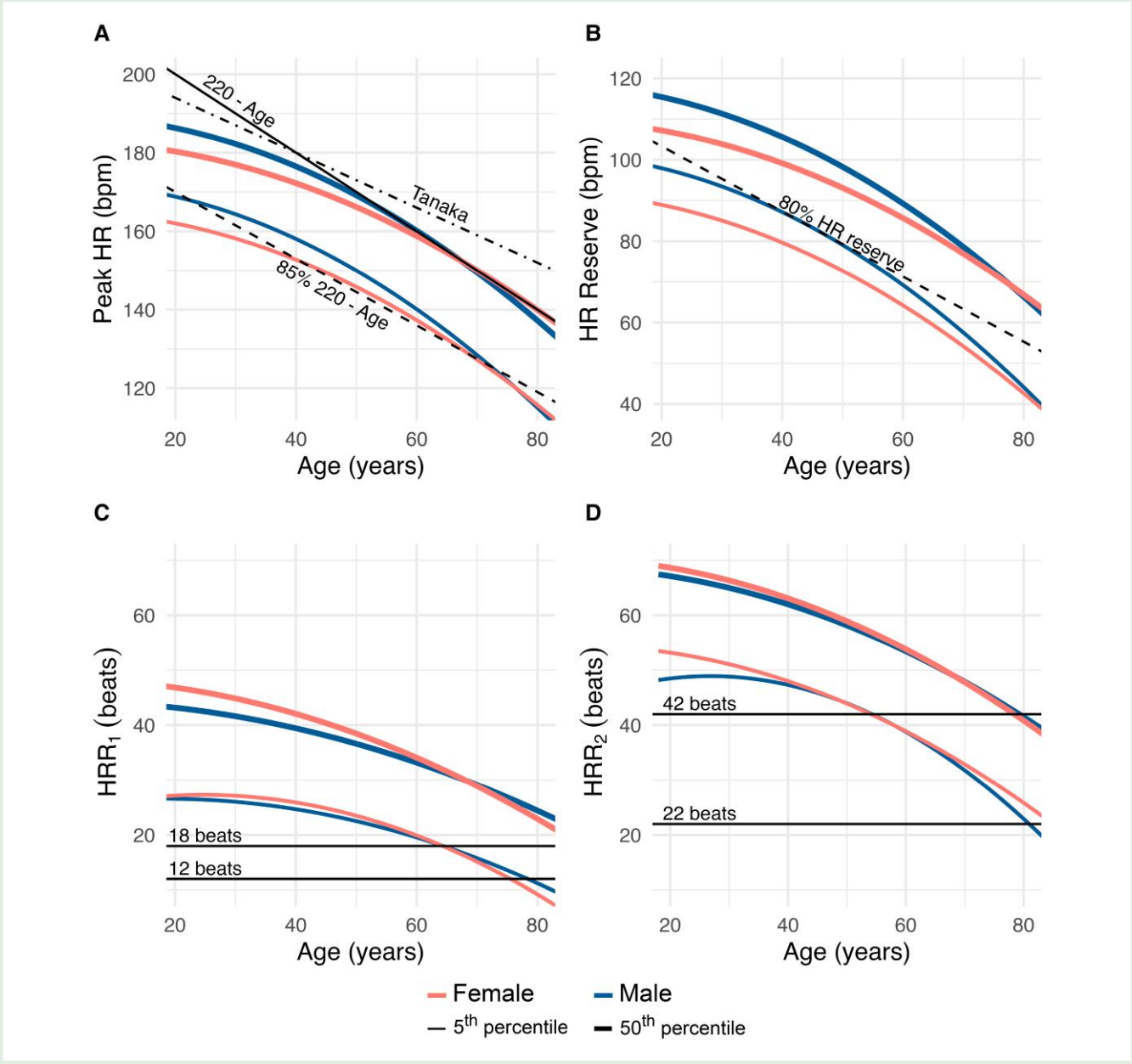


Figure 2 Age- and sex-specific 5th and 50th percentiles for peak HR (*A*), HR reserve (*B*), HRR_1 (*C*), and HRR_2 (*D*) obtained in cycle exercise testing in 1383 males and 859 females aged 18–85 years. The thinner and thicker curvilinear lines represent the 5th and 50th percentiles, respectively, for males and females. The solid black line represents the 220 − age equation, the dash-dotted line represents Tanaka's equation and the dashed line represents 85% of the 220 − age equation (*A*). The dashed line represents 80% of HR reserve (*B*). The solid lines represent HRR_1 thresholds of 12 and 18 beats (*C*) and HRR_2 thresholds of 22 and 42 beats (*D*). HR, heart rate; HR reserve, heart rate reserve; HRR_1, heart rate recovery at 1 min post-exercise; HRR_2, heart rate recovery at 2 min post-exercise.

of the HR variables was found for all-cause and CV mortality. Blunted HR recovery variables were the numerically strongest predictors of all-cause mortality. However, no single HR index was found to be significantly superior in predicting CV. The combination of blunted HR indices numerically increased the risk of all-cause [HRR_1 and HRR_2, 1.96 (1.68–2.29), and peak HR and HRR_1, 1.87 (1.56–2.23)] and CV mortality, although no specific combination was superior for predicting CV mortality (*Table 3*). A bootstrap analysis (1000 iterations) confirmed the predictive value of HR recovery variables, with results consistent across resamples (see Supplementary material online, *Figure S5*).

The bootstrap results indicated that HRR_1 had the highest hazard ratio for all-cause mortality: it was higher than peak HR and HRR_2 in 99.8 and 87.6% of iterations, respectively. HRR_1 also had the highest hazard ratio for non-CV mortality, being higher than peak HR and HRR_2 in 100 and 95.7% of iterations, respectively, in cause-specific Cox regression analysis, and higher than peak HR and HRR_2 in 99.9 and 85.3% of iterations, respectively, in sub-distribution Cox regression analysis. For CV mortality, HRR_2 had the highest hazard ratio: it was higher than peak HR and HRR_1 in 74.5 and 70.2% of iterations, respectively, in cause-specific Cox regression analysis, and higher than peak HR and HRR_1 in 59 and

Table 1 Quantile regression models (5th percentile and 50th percentile), sex-stratified for predicting peak HR and HR reserve, and unisex for HRR_1 and HRR_2 in a cycle exercise test

	Constant	Age	Age^2	Resting HR	BMI
Peak HR					
5th					
Male	179.1		−0.0090	0.31	−1.12
Female	151.5		−0.0077	0.65	−1.39
50th					
Male	182.0		−0.0082	0.32	−0.59
Female	172.5		−0.0067	0.30	−0.47
HR reserve					
5th					
Male	179.1		−0.0090	−0.69	−1.12
Female	151.5		−0.0077	−0.35	−1.39
50th					
Male	182.0		−0.0082	−0.68	−0.59
Female	172.5		−0.0067	−0.70	−0.47
HRR_1					
5th	36.4	0.26	−0.0051	−0.19	
50th	69.1		−0.0033	−0.21	−0.34
HRR_2					
5th	73.3	0.38	−0.0078	−0.26	−0.39
50th	102.8		−0.0044	−0.31	−0.44

HR, heart rate; HRR_1, heart rate recovery at 1 min post-exercise; HRR_2, heart rate recovery at 2 min post-exercise.

85.3%, respectively, in sub-distribution Cox regression analysis. A paired *t*-test confirmed that all differences were significant ($P < 0.001$).

Blunted peak HR was an equally strong predictor of all-cause mortality as 85% age-predicted maximal HR [hazard ratio 1.29 (95% confidence interval, 1.11–1.50)] and a similar predictor of all-cause mortality as 80% reserve used [1.36 (1.17–1.57)]. In a multivariate adjusted analysis where all HR response and HR recovery continuous variables were included in the model, only HRR_1 remained a significant predictor for all-cause mortality [0.98 (0.97–0.99)].

Sensitivity analysis in subjects with normal exercise capacity

Normal exercise capacity was achieved in 8070 subjects according to Brudin *et al.*[19] A sub-analysis limited to these subjects revealed that all blunted HR indices remained strong predictors of all-cause mortality [HRR_1, 1.96 (1.61–2.39), HRR_2, 1.76 (1.46–2.12), and peak HR, 1.72 (1.40–2.11)] even in the presence of normal exercise capacity.

Sensitivity analysis for beta-blocker use

The overall prevalence of beta-blocker use was 22% in males and 23% in females (see Supplementary material online, *Table S3*). There was a 37% prevalence of beta-blocker use in subjects with CV risk without established disease and 54% in subjects with CV disease. Our findings indicated that the use of beta-blockers had slightly higher impact on HR response variables than on HRR_1 and HRR_2, although all the HR responses were significantly reduced when beta-blockers were used (see Supplementary material online, *Table S3*). A sub-analysis limited to subjects not using beta-blockers ($N = 7683$) revealed, in general, similar prognostic value of peak HR, HRR_1, and HRR_2 for all-cause mortality [1.48 (1.23–1.79), 1.65 (1.38–1.98), and 1.71 (1.43–2.04), respectively] compared with the overall population.

Discussion

This study presents the largest up-to-date reference equations for HR response (peak HR and HR reserve) and HR recovery at 1 and 2 min (HRR_1 and HRR_2) in cycle exercise testing in people aged 18–85 years. We confirmed that blunted peak HR (and HR reserve) and blunted HRR_1 and HRR_2 obtained at symptom-limited cycle exercise testing are independent predictors of all-cause and CV mortality. Specifically, blunted HRR_1 emerged as the strongest predictor for all-cause mortality and remained the strongest predictor of all-cause mortality in individuals with normal exercise capacity. Lastly, the combination of blunted HR indices appeared to add prognostic value in all the analyses.

Normal values for heart rate response and recovery

In our reference population, peak HR differed from that suggested by the 220 − age equation, especially in young adults, in line with other reports.[15] However, our age- and sex-specific LLN peak HR was largely in agreement with 85% of the age-predicted maximal HR (based on the 220 − age equation).[6] We observed a progressively lower mean peak HR as age increased compared with Tanaka's equation,[15] although this difference was significantly reduced when using only age in the prediction equation. Another possible explanation for this difference in peak HR could be that the CV and autonomic responses are higher when utilizing a treadmill compared with a cycle ergometer.[23] The sex difference is in line with Gläser *et al.*,[24] up to 50 years, but was not confirmed in Tanaka's meta-analysis.[15]

The commonly used reference values for HR recovery obtained from treadmill exercise tests are fixed thresholds despite the age-dependent response. For instance, the established thresholds for HRR_1 are set at 12 beats with a cool-down period post-exercise[7] and 18 beats with an immediate supine resting position.[10] Similarly, thresholds for HRR_2 are set at 22 beats in maximal exercise testing with an immediate supine resting position in subjects with CV disease[11] and at 42 beats in submaximal exercise testing with an immediate seated resting position in subjects without CV disease.[12] We propose novel age-specific reference values (LLN HRR_1 and LLN HRR_2) that adjust for the age dependency of HR recovery, which diverge notably from the values reported in the abovementioned literature.

There was an increasing trend in HR response as the metabolic demand increased in our reference population. This may suggest the involvement of different autonomic mechanisms in specific exercise phases, as previously suggested,[25] although an alternative explanation could be the additional compensatory mechanism to sustain further increase in cardiac output beyond the point of stroke volume plateau.[26] Heart rate recovery kinetics displayed the fastest HR decrease within the first minute post-exercise. The rapid recovery phase has been previously reported to be predominantly promoted by vagal reactivation, while the slower phase is thought to be due to a combination of parasympathetic tone and sympathetic withdrawal.[3]

Blunted heart rate response and recovery in relation to mortality

Blunted peak HR (and HR reserve), HRR_1, and HRR_2 were associated with all-cause and CV mortality in the overall population. Peak HR

Table 2 HR response and HR recovery values and CV and non-CV mortality in the overall population

	Survived $N = 8807$	CV death $N = 367$	Non-CV death $n = 699$	P test
Age, years[a]	56.0 (14.4)	71.6 (8.8)	69.2 (9.8)	<0.001*
Sex[b]				
Female	4062 (46.1)	147 (40.1)	291 (41.6)	0.007*
Male	4745 (53.9)	220 (59.9)	408 (58.4)	
CV risk factor group[b]				
1	4400 (50.0)	52 (14.2)	159 (22.7)	<0.001*
2	3108 (35.3)	163 (44.4)	339 (48.5)	
3	1299 (14.7)	152 (41.4)	201 (28.8)	
Resting HR, b.p.m.[a]	74.1 (12.9)	72.2 (12.8)	74.6 (13.6)	0.010[c]
Peak HR, b.p.m.[a]	154.0 (22.7)	124.3 (22.1)	132.1 (21.9)	<0.001*
Per cent predicted maximal HR, %[a]	93.8 (10.9)	83.7 (14.0)	87.6 (13.3)	<0.001*
HR reserve, b.p.m.[a]	79.9 (22.1)	52.1 (18.1)	57.5 (20.6)	<0.001*
HR response category[b]				
Normal	7312 (83.0)	192 (52.3)	428 (61.2)	<0.001*
Blunted	1495 (17.0)	175 (47.7)	271 (38.8)	
HRR_1, beats[a]	31.3 (12.1)	18.4 (9.7)	19.9 (11.3)	<0.001*
Per cent predicted HRR_1, %[a]	93.8 (31.8)	67.6 (34.6)	70.6 (36.6)	<0.001*
HRR_1 category[b]				
Normal	7764 (88.2)	238 (64.9)	461 (66.0)	<0.001*
Blunted	1043 (11.8)	129 (35.1)	238 (34.0)	
HRR_2, beats[a]	49.9 (14.7)	32.1 (13.2)	35.1 (14.7)	<0.001*
Per cent predicted HRR_2, %[a]	93.5 (24.1)	71.1 (29.1)	75.5 (28.9)	<0.001*
HRR_2 category[b]				
Normal	7456 (84.7)	202 (55.0)	426 (60.9)	<0.001*
Blunted	1351 (15.3)	165 (45.0)	273 (39.1)	
Per cent predicted exercise capacity, %[a]	92.0 (17.4)	74.9 (16.5)	78.0 (17.8)	<0.001*

HR, heart rate; HRR_1, heart rate recovery at 1 min post-exercise; HRR_2, heart rate recovery at 2 min post-exercise; b.p.m., beats per minute.
[a]Mean ± (SD).
[b]*N* (%). CV risk factor group: 1 (CV risk-free), 2 (CV risk factors without established CV diagnoses), and 3 (established CV disease).
[c]No difference between survived and non-CV death.
*Bonferroni post-hoc with $P < 0.05$ between all three categories (survived, CV death, and non-CV death).

findings are in line with the previous reports,[2] as HR contributes greatly to the overall increase in oxygen uptake during exercise, together with increase in stroke volume and peripheral oxygen extraction. Chronotropic incompetence in individuals without the ability to compensate with these other mechanisms will be associated with decreased exercise capacity, which is also independently associated with mortality.[2,20] The use of 85% age-predicted maximal HR could facilitate clinical interpretation of chronotropic response as it correlates well with LLN peak HR. Our results are in concordance with previous studies outlining HR response as a predictor of mortality.[8,27] Engeseth *et al.*[28] reported HR reserve had prognostic value in unfit males but not in males with normal exercise capacity, suggesting an association between impaired balance of autonomic tone, impaired HR response, and CV incidence interlinked to exercise capacity.

Blunted HR recovery variables were the strongest predictors of all-cause mortality (HRR_1 followed by HRR_2). Previous studies utilizing cycle ergometers have assessed outcome in relation to the existing HR recovery thresholds. HRR_1 12 b.p.m. threshold was confirmed to be independent predictor of mortality in survivors of acute myocardial infarction.[29] Sipilä *et al.*[30] corroborated the HRR_1 18 b.p.m. threshold to be an independent predictor of mortality in referred population,[10] and Jouven *et al.*[31] suggested 25 b.p.m. as a threshold for asymptomatic and CV risk-free men. Our results support the finding that subjects with CV disease generally exhibit decreased performance and diminished HR response and recovery compared with apparently CV risk-free subjects. Furthermore, our findings demonstrate an inverse correlation with HR responses and the number of CV risk factors, consistent with the results reported by Laforgia *et al.*[32] Pierpont *et al.*[33] suggested that not only reduced exercise capacity but also systemic and chronic autonomic changes present in CV disease could contribute to decreased parasympathetic tone and increase in basal sympathetic activity, further impairing HR recovery. Thus, the primary association of HR recovery with the autonomic nervous system,[33] its negligible correlation with exercise capacity, and weak correlation to peak HR could explain why HRR_1 remains the strongest predictor of all-cause mortality after adjustment for exercise capacity. Furthermore, HR recovery is dependent on the type of exercise, and therefore, method standardization is needed to facilitate HR recovery evaluation.[3,33,34] Our findings of HR recovery are in line with the meta-analysis of Qiu *et al.*[35] and with previous treadmill studies in multiple cohorts, where HRR_1 was found to be a strong and independent predictor of mortality even after adjustments for exercise capacity, coronary angiography results, left ventricular function,

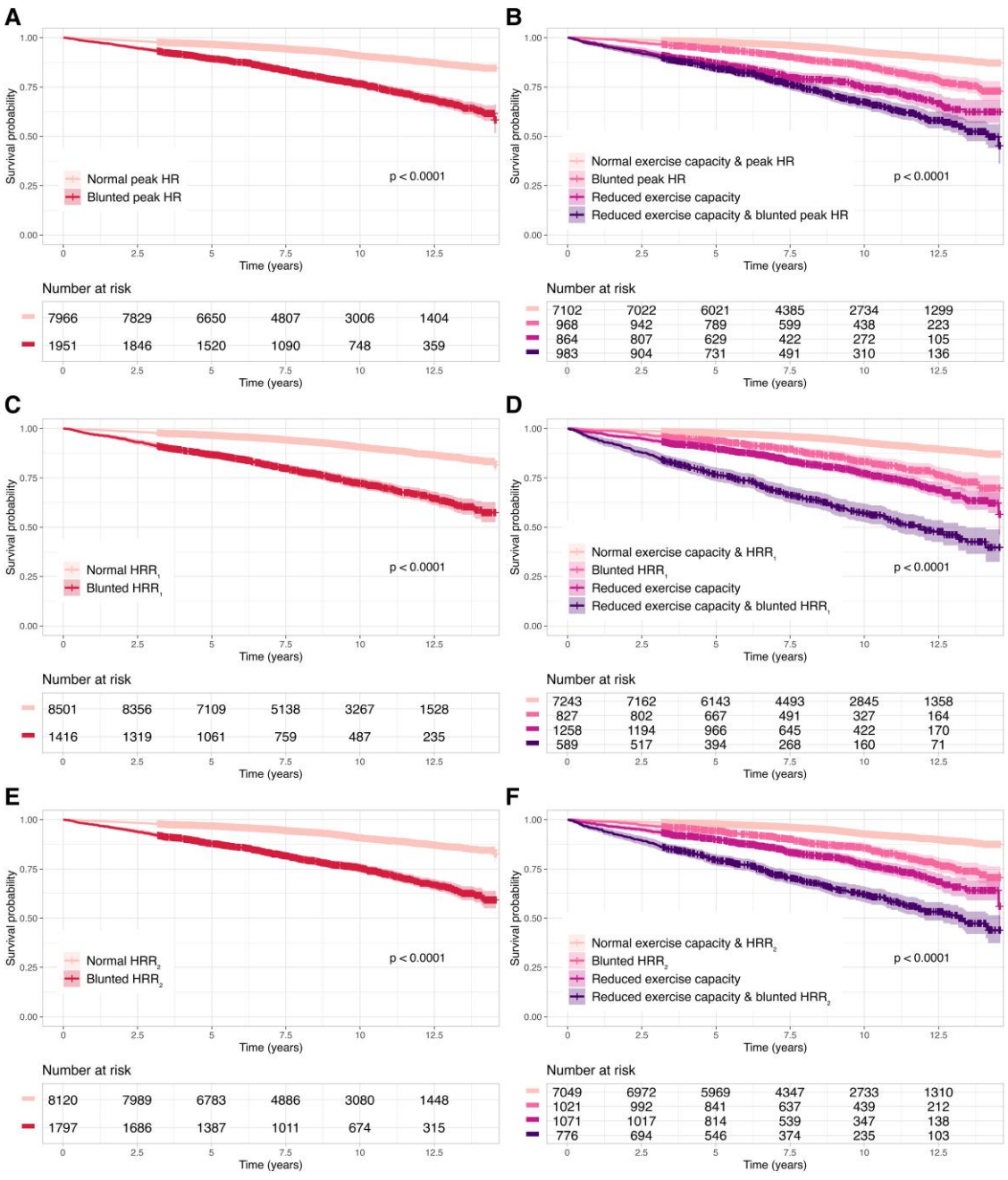


Figure 3 Kaplan–Meier survival curves with a median of 8.6-year cumulative survival analysis for normal and blunted values for peak HR (*A*), HRR_1 (*C*), and HRR_2 (*E*), as well as for combinations of exercise capacity characteristics with peak HR (*B*), HRR_1 (*D*), and HRR_2 (*F*). HR, heart rate; HRR_1, heart rate recovery at 1 min post-exercise; HRR_2, heart rate recovery at 2 min post-exercise.

ventilatory efficiency slope, and other cardiopulmonary exercise test variables.[13,36,37] Heart rate recovery indices appeared to remain prognostic for mortality regardless of beta-blocker use in line with Arena *et al.*[38] Blunted HR recovery and peak HR remained predictors of all-cause mortality even in subjects with normal exercise capacity, underscoring the importance of routinely evaluating HR recovery variables in clinical settings, as they can contribute significantly to risk stratification in standard cycle exercise testing. However, Sydó *et al.*[39] described reduced utility of HRR_1 in patients taking beta-blockers and those with normal cardiorespiratory fitness. Previous studies have reported that HR recovery variables remain predictors of mortality in submaximal efforts, suggesting that HR recovery is mainly driven by the parasympathetic tone reactivation in the rapid recovery phase.[12,40] Therefore, HR recovery assessment should remain a robust measure even in individuals taking beta-blockers, not achieving maximal effort, or with normal exercise capacity, as it retains prognostic value.

Lastly, the combination of blunted HR indices appeared to add prognostic value for all-cause and CV mortality. Our mortality risk prediction

Table 3 Risk of all-cause mortality in Cox multivariable regression analysis and incidence of CV and non-CV mortality by blunted (<5th percentile) peak HR, HRR_1, and HRR_2, and their combinations

	All-cause mortality	CV and non-CV mortality			
	Cox Regression	Sub-distribution hazard model		Cause-specific hazard model	
Variables		CV death	Non-CV death	CV death	Non-CV death
Blunted peak HR	1.32 (1.14–1.52)	1.55 (1.20–1.99)	1.26 (1.04–1.53)	1.51 (1.18–1.93)	1.29 (1.08–1.55)
Blunted HRR_1	1.70 (1.49–1.94)	1.39 (1.10–1.77)	1.81 (1.51–2.16)	1.52 (1.21–1.92)	1.84 (1.56–2.18)
Blunted HRR_2	1.57 (1.37–1.79)	1.59 (1.25–1.99)	1.57 (1.32–1.87)	1.64 (1.30–2.06)	1.61 (1.36–1.91)
HRR_1 and HRR_2					
Only blunted HRR_1	1.36 (1.06–1.74)	0.81 (0.48–1.37)	1.73 (1.27–2.34)	0.84 (0.50–1.41)	1.64 (1.23–2.20)
Only blunted HRR_2	1.24 (1.02–1.50)	1.29 (0.93–1.79)	1.30 (1.01–1.66)	1.24 (0.90–1.71)	1.28 (1.01–1.63)
Both blunted	1.96 (1.68–2.29)	1.72 (1.31–2.26)	2.00 (1.62–2.45)	1.90 (1.46–2.47)	2.08 (1.71–2.53)
Peak HR and HRR_1					
Only blunted peak HR	1.20 (1.00–1.43)	1.46 (1.07–1.98)	1.17 (0.93–1.48)	1.37 (1.02–1.85)	1.19 (0.95–1.49)
Only blunted HRR_1	1.73 (1.42–2.12)	1.27 (0.86–1.87)	1.96 (1.55–2.52)	1.40 (0.96–2.04)	1.95 (1.54–2.47)
Both blunted	1.87 (1.56–2.23)	1.82 (1.33–2.49)	1.86 (1.38–2.38)	1.93 (1.43–2.61)	1.96 (1.56–2.46)
Peak HR and HRR_2					
Only blunted peak HR	1.12 (0.91–1.37)	1.30 (0.91–1.85)	1.07 (0.82–1.41)	1.23 (0.86–1.76)	1.09 (0.83–1.41)
Only blunted HRR_2	1.56 (1.27–1.92)	1.38 (0.94–2.02)	1.62 (1.26–2.08)	1.46 (1.00–2.12)	1.64 (1.27–2.11)
Both blunted	1.64 (1.39–1.94)	1.85 (1.39–2.47)	1.59 (1.27–1.99)	1.87 (1.41–2.47)	1.65 (1.34–2.03)

Medical-related deaths ($N = 1066$), CV-related deaths ($N = 367$), and non-CV–related deaths ($N = 699$). Fully adjusted model: adjusted for age, sex, BMI, exercise capacity, resting HR, cardiovascular risk factors, and use of beta-blockers.
HR, heart rate; HRR_1, heart rate recovery at 1 min post-exercise; HRR_2, heart rate recovery at 2 min post-exercise.

model indicates that individuals with a combination of impaired HR indices have approximately two-fold higher risk of all-cause and CV mortality than those with normal values. This supports previous findings that the combination of HR response and HR recovery variables is a stronger predictor than either of the variables alone.[9,18,41]

The main strengths of this study are the large number of included subjects and the long-term follow-up through national patient registries to identify all-cause and CV mortality. No expired gas analysis was used, meaning neither maximal oxygen uptake nor respiratory exchange ratio was available to objectively quantify the maximal effort. However, the levels of rated perceived exertion achieved here are relevant for clinical exercise tests, as we limited the analyses to subjects achieving at least a Borg scale of 17.

In Sweden and other European countries, a standard cycle exercise test generally consists of an initial workload followed by a continuous ramp increment until maximal exertion and a recovery phase conducted in a supine position with no cool-down period that allows for a greater HR recovery compared with other protocols. Therefore, we acknowledge that the present reference equations for HR recovery might be less relevant for protocols where the subject remains sited on the cycle at the end of exercise.[4] We lacked information on smoking and physical activity habits but were able to adjust for other potential confounders provided in the detailed subject baseline characteristics, and we had complete exercise test data. Inclusion of subjects using beta-blockers can be regarded as a limitation, as beta-blockers affect mainly HR response and also HR recovery. However, the use of beta-blockers is common in patients referred for exercise stress testing, and adjusted analyses for beta-blocker use did not significantly impair the prognostic value of HR indices in the overall population. Additionally, our results have not been externally validated, which would have strengthened our findings.

Conclusion

Based on this study, we propose age-dependent novel reference values for HR responses, particularly HR recovery (HRR_1 and HRR_2), and confirm that all blunted HR indices are strong predictors of all-cause and CV mortality in patients referred for exercise cycle testing. Heart rate recovery variables emerged as the strongest predictors of all-cause mortality, even among subjects with normal exercise capacity, underscoring the crucial role of HR recovery in mortality risk assessment. However, no single HR index was found to be significantly superior in predicting CV mortality. Additionally, the combination of blunted HR indices appeared to add prognostic value in all analyses. Further research is needed to evaluate the prognostic significance of additional indices derived from cycle exercise testing.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

All authors contributed to the conception or design of the study. L.B. acquired the data and managed the database together with M.E. J.J. performed statistical analyses under the supervision of A.M. and statistician X.Z. J.J. drafted the manuscript under the supervision of A.M. All authors critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article cannot be shared publicly due to the inclusion of personal health data requiring separate approval by the Swedish Ethical Review Authority.

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