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Resting heart rate in late adolescence and long term risk of cardiovascular disease in Swedish men

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ABSTRACT

Aim: To investigate the association of resting heart rate (RHR) measured in late adolescence with the long term risk of myocardial infarction (MI), ischemic stroke (IS), heart failure (HF), atrial fibrillation (AF), cardiovascular- and all-cause death.

Methods and results: We followed a cohort of Swedish men enrolled for conscription in 1968–2005 (n = 1,008,485; mean age = 18.3 years) until December 2014. Outcomes were collected from the national inpatient - (IPR), outpatient - (OPR) and cause of death registries. Cox proportional hazard models were used to analyze the longitudinal association between RHR and outcomes while adjusting for potential confounders. While we found no independent association between RHR and risk of IS or MI when comparing the highest with the lowest quintile of the RHR distribution, but a positive association persisted between RHR and incident HF (Hazard ratio (HR) = 1.39 [95% confidence interval (CI) = 1.29–1.49]) after adjustment for body mass index (BMI) and blood pressure (BP). In similarly adjusted models, an inverse association was found for AF while there were weaker associations with death from cardiovascular disease (CVD) and all causes (adjusted HR = 1.12 [CI = 1.04–1.21] and 1.20 [CI = 1.17–1.24]). After further adjustment for cardiorespiratory fitness (CRF), the associations persisted for HF (HR = 1.26 [1.17–1.35] for any diagnostic position and HR = 1.43 [1.28–1.60] for HF as a main diagnosis) and for all-cause death (HR 1.09 [1.05–1.12]) but not for CVD death.

Conclusion: Adolescent RHR is associated with future risk of HF and death, independently of BP, BMI and CRF, but not with CVD death, MI or IS, suggesting a causal pathway between elevated heart rate and myocardial dysfunction.

1. Introduction

Although progress in the prevention and treatment of cardiovascular disease (CVD) has led to decreasing trends in mortality in Sweden and many other western high-income countries, CVD persists as the main cause of death world-wide, accountable for approximately 30% of all deaths [1]. Despite some inconsistencies, single measures of resting heart rate (RHR) have previously been shown to associate with other cardiovascular risk factors [2–4], all-cause and cardiovascular mortality as well as non-fatal cardiovascular outcomes [5–10]. Longitudinal changes in RHR have also been found to predict CVD and death independently of traditional risk factors [11]. Cardiorespiratory fitness (CRF) is known to be protective of CVD, and is inversely associated with RHR [12]. It has previously been found that aerobic conditioning may attenuate the sympathetic overactivity associated with heart failure (HF) [13]. Because of this, CRF is an important factor to consider that may otherwise confound the associations investigated.

Previous studies of the relationship between RHR and cardiovascular outcomes have mainly been carried out in middle-aged or older subjects [5–10]. This limits conclusions because of potential reverse causality, as preexisting or subclinical CVD may lead to elevated RHR. In the present study, we investigated the effect of RHR on future cardiovascular outcomes in healthy adolescents, with special consideration of the potential

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effect of CRF. For this purpose, we used data from the Swedish Military Service Conscription Registry, containing data on approximately 1.8 million Swedish men. Data from the Swedish National Inpatient Registry (IPR), Outpatient Registry (OPR), and Cause of Death registries were used for follow-up with respect to cardiovascular outcomes.

2. Methods

2.1. Participants

As demanded by law, all Swedish men enlisted for military service from 1901 to 2005. Exemptions were made only for those with severe medical- or mental conditions or disabilities (2–3% each year). The original cohort consisted of all men born between the years 1950 and 1987, who enlisted for military service in 1968–2005 (n = 1,874,651) (Fig. 1). We excluded men who enlisted early or late (age < 16 or >25 years; n = 57,095) and those with missing data on RHR (n = 633,930) or values >145 and <35 (n = 493), as well as those with missing values for CRF (n = 23,275) and BMI (n = 150,662). Possibly due to errors in registering procedures, RHR data was nearly completely missing through the years 1984 and 1994, constituting the absolute majority of missing values (n = 558,985). We excluded men with invalid systolic and diastolic blood pressure (BP) and values that could be considered outliers or errors in measurement and registration (>(75th centile + 3 × interquartile range) and < (25th centile − 3 × interquartile range)) (n = 503). Those with pre-existing diagnoses of CVD (n = 208) were also excluded. In all, 1,008,485 conscripts were included in the study. The regional ethics committee of the University of Gothenburg approved the study, which was conducted in accordance with the declaration of Helsinki.

2.2. Conscription register data

From 1968 through 2005, all conscripts underwent a two-day standardized enlistment protocol that involved both physical and psychological evaluations by a physician and a psychologist. Conscripts were measured for height and weight. Morbidities were recorded. RHR and BP were measured after 5 to 10 min of rest in supine position with an appropriately sized cuff at heart level. As part of the physical evaluation, CRF was measured using a stationary bicycle ergometer; maximum work capacity expressed in Watts (Wmax) was thereafter divided by body weight and transformed into a standard nine (stanine) scores (1–9) [14]. For further information, see supplementary material.

2.3. Follow-up procedures

Diagnoses at discharge are mandatorily reported to the national Inpatient Registry (IPR). Register coverage increased gradually over the period 1968–1986 and is considered complete from 1987. From 2001 it also contains records of patients in hospital outpatient care (OPR). The 12-digit personal identification number given to all Swedish residents allowed for linkage of national registers (the Swedish Military Service Conscription Registry, the IPR, the OPR, and the Cause of Death registry).

Participants were followed from date of conscription to the point of discharge after hospitalization for CVD, or death, registered in the IPR and cause of death registries according to the International Classification of Diseases (ICD). From 1968 to 1986 ICD-8 was in use; from 1987 to 1996, ICD-9; and thereafter, ICD-10. Incident myocardial infarction (MI) was defined by 410 (ICD-8 and -9) and I21 (ICD-10); ischemic stroke (IS) by 433, 434, 436 (ICD-8), 434, 436 (ICD-9), and I63, I64 (ICD-10); heart failure (HF) by 427.00 and 427.10 (ICD-8), 428 (ICD-9), and I50 (ICD-10); atrial fibrillation (AF) by 427.92 (ICD-8), 427D (ICD-9), and I48 (ICD-10). The following preexisting comorbidities recorded at baseline were included: diabetes 250 (ICD-8 and -9) and E10-E14 (ICD-10); hypertension 401–405 (ICD-8 and -9) and I10-I15 (ICD-10); alcohol-related disorders 291, 303 (ICD-8), 291, 303, 305.0 (ICD-9), and F10 (ICD-10); other substance use disorders 294.3, 304 (ICD-8), 292, 304, 305.1–8 (ICD-9), and F11-F19 (ICD-10).

2.4. Statistical methods

Incidence rates and their corresponding 95% confidence intervals (CI) were calculated using Poisson regression. We used Cox proportional hazards regression to estimate

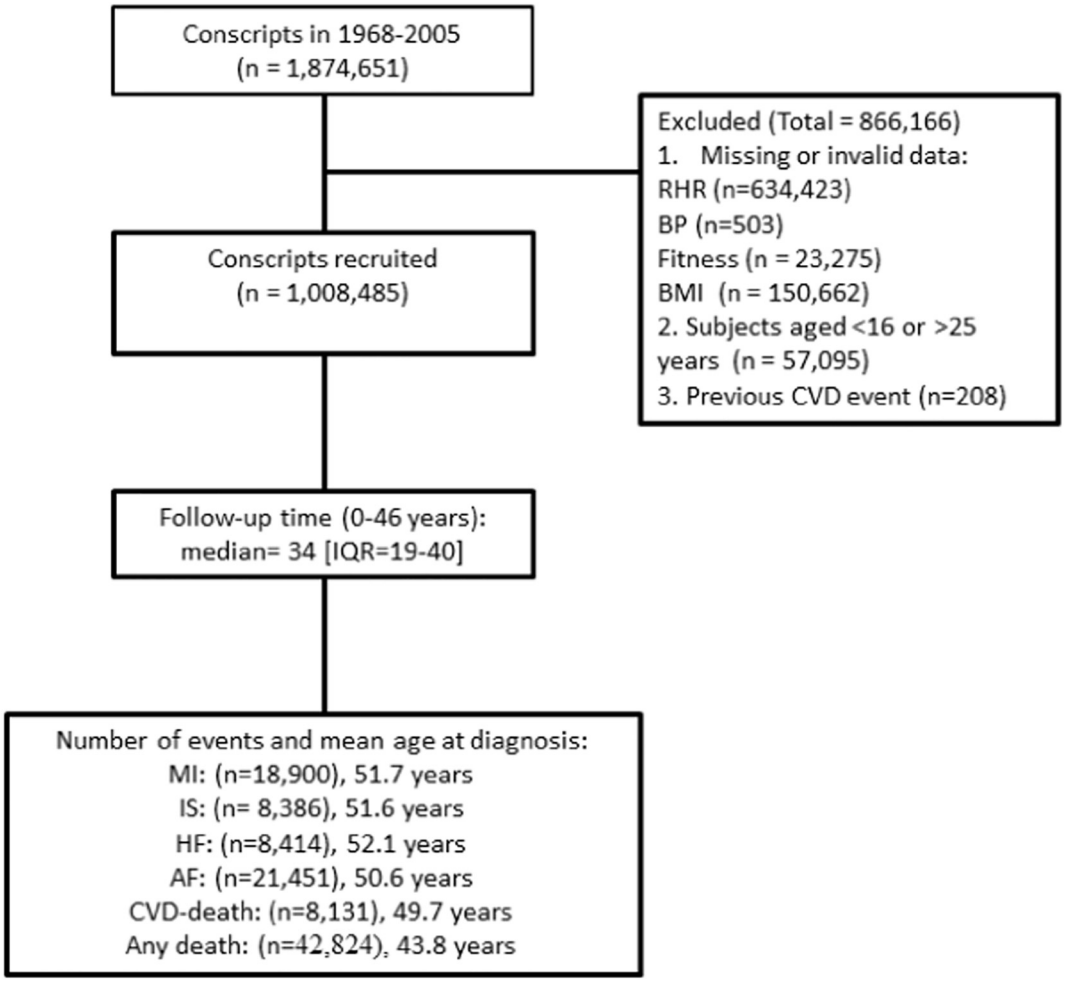

Fig. 1. Flow chart of included and excluded conscripts, based on recommendations in strengthening the reporting of observational studies in epidemiology [48]. The figure shows median years of observation (follow-up time) with corresponding interquartile range (IQR), numbers of incident cases for each study outcome and mean age at diagnosis. Abbreviations: resting heart rate (RHR), blood pressure (BP), body mass index (BMI), heart failure (HF), ischemic stroke (IS), acute myocardial infarction (MI), atrial fibrillation (AF).