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Long-Term Change in Cardiorespiratory Fitness in Relation to Atrial Fibrillation and Heart Failure (From the Kuopio Ischemic Heart Disease Risk Factor Study)

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The benefits of aerobic fitness in relation to all-cause and cardiovascular mortality is well established; however, the associations of long term change in cardiorespiratory fitness with incident heart failure (HF) and atrial fibrillation (AF) have not been studied before. The Kuopio Ischaemic Heart Disease Risk Factor Study is a prospective cohort comprising men aged 42 to 60 years from the city of Kuopio and its surroundings with a baseline examination between 1984 and 1989 (V1), a re-examination at 11 years (V2), and up to 15 years of follow-up from V2. Cardiorespiratory fitness (CRF), as assessed by VO_2max, was measured at both visits using respiratory gas exchange during maximal exercise tolerance test. The difference (ΔVO_2max) was estimated as VO_2max (V2) - VO_2max (V1). Participants with no missing data on both baseline and 11-year exercise test were included (N=481). The mean ΔVO_2max was -5.4(SD 5.4) ml/min*kg. During a median follow-up of 14.3 (interquartile range: 13.3–15.1) years, 46 (9.6%) incident HF and 73 (15.2%) incident AF events were recorded. In a multivariate analysis adjusted for baseline age, baseline VO_2max, systolic blood pressure, smoking, type 2 diabetes and cardiovascular disease, per 1 ml/min*kg higher ΔVO_2max was log linearly associated with incident HF with a 10% relative risk reduction of HF (HR 0.90; 95% CI: 0.83 to 0.97). No significant relationship of ΔVO_2max with incident AF was observed. **I**n Conclusion, overall long-term improvement in CRF is associated with reduced risk of HF, indicating the importance of maintaining good CRF over time.

Key words: Cardiorespiratory fitness; maximal oxygen uptake; atrial fibrillation; heart failure

The association between CRF and mortality has been proposed to persist across the lifetime, with improvement in CRF linked to significant improvement in overall survival. However, few studies have assessed the relationship between changes in CRF over time and risk of mortality[1–3], while none have investigated the health benefits, beyond overall survival advantage that any improvement in fitness across life span may have for both HF or AF. In addition, most of the prior studies assessing overall survival, have relied on an indirect estimation of CRF (i.e., treadmill time) [1,2] or exercise-test based fitness scores[3]. The present study aims to evaluate in detail, the prospective associations of long-term change in directly measured CRF with incident HF and AF in a population-based sample of men from eastern Finland.

Methods

The study population is a representative sample of men living in the city of Kuopio and its surrounding rural communities in Eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study, a longitudinal population-based study designed to investigate risk factors for CVD and related outcomes. Participants were 42-61 years of age during baseline examinations, performed between March 20, 1984 and December 5, 1989. Of 3,235 potentially randomly selected eligible men, 2,682 (82.9%) volunteered to participate in this study, 186 did not respond to the invitation, and 367 declined to give informed consent. After baseline examinations, repeat assessments were performed in a random sample of participants at year 11. The present analysis is based on 481 men with no missing data on exercise test and covariates, and who had assessments of CRF at baseline and 11-year examination (mean time interval 11.1 (standard deviation, SD 0.37) years). Supplement table 1 shows participant characteristics of those included and not included in the analysis. The study was approved, by the Research Ethics Committee of the University of Eastern Finland, and each participant gave written informed consent.

Maximal oxygen uptake was used as a measure of CRF, which was assessed using a respiratory gas exchange analyzer during maximal symptom-limited cycle ergometer exercise tolerance test. The standardized testing protocol comprised of a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min with the direct analyses of respiratory gases (Medical Graphics, St. Paul, Minnesota), and the VO_2max was defined as the highest value for or the plateau of oxygen uptake[4,5]. The assessment of CRF was performed at baseline and repeated at 11-year examination.

A subject was defined a smoker if he had ever smoked on a regular basis. Resting blood pressure was measured between 8:00 and 10:00 AM with a random-zero sphygmomanometer. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory [5]. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Diabetes was defined as a fasting blood glucose level ≥7.0 mmol/L or clinical diagnosis of diabetes with dietary, oral, or insulin treatment. The collection of blood specimens and the measurement of serum lipids, lipoproteins, creatinine and glucose have been described elsewhere[6]. Serum C-reactive protein was measured with an

immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, CA, U.S.A.).

All incident HF and AF cases that occurred from the second CRF assessment (March 2000 and December 2001) through 2013 were included. There were no losses to follow-up. All study participants are under continuous surveillance for the development of new CVD events, including new incident HF cases. The sources of information on HF were based on hospital records and medico-legal reports.The diagnostic classification of HF cases were coded according to *the International Classification of Disease, Tenth Revision* (*ICD-10*) *codes* (I00-I99) and (I50.0-I50.9, I11, I42.0-I42.9). The diagnosis of HF was based on a previous history of heart disease, physical examination by a doctor, laboratory investigations including the determination of NT-proBNP, echocardiography as well as ECG findings. Incident AF was identified by comprehensive review of hospital discharge diagnoses, inpatient physician claims data, and study ECGs. All AF events that occurred between March 2005 and December 2010 were included. Atrial flutter was included as AF case. Data on events were obtained by record linkage from the national computerized hospitalization registry, which covers every hospitalization in Finland. The definition of AF used in this study concerns hospitalized patients in whom a diagnosis of AF was based on electrocardiography. Diagnosis of AF was obtained also from patients at the outpatient clinic or the hospital department. There were 29 patients with incident AF who had also HF, nine with ischemic stroke and 14 with acute MI at the same time. These outcomes were also included in the study. The diagnosis of AF was coded according to International Classification of Diseases codes. To verify the accuracy of the register-linked diagnoses, records including electrocardiography were checked by a physician [7]. Data on incident acute coronary events and deaths were obtained by computer linkage to the national hospital discharge and death certificate registers.

Descriptive data are presented as means and SD for continuous variables and numbers and percentages for categorical ones. Time-to-event analyses were conducted using Cox proportional hazards models to examine the association of ΔCRF (difference between CRF value at 11 years and baseline) with incident HF after confirming that the assumption of proportionality of hazards was met. Cardiorespiratory fitness was modeled both as continuous (per 1 ml/kg/min and MET increase, where 1 MET corresponds to 3.5 ml/kg/min change in VO2max) and categorical (tertiles) variables. All models were adjusted for age and baseline cardiorespiratory fitness (VO2max) and subsequently adjusted for additional potential confounders (systolic blood pressure (SBP), history of CVD, diabetes, smoking status, resting heart rate, and left ventricular hypertrophy) selected on the basis of their previously established role as risk factors. To evaluate whether ΔCRF predicted HF and AF independently of incident coronary events during follow-up, we adjusted for incident acute coronary events, fitting these as a time-dependent covariate. We also performed additional analyses modeling any death as a competing outcome to HF and AF respectively. The shape of the association with HF and AF risk was assessed by plotting hazard ratios (HRs) calculated within quintiles of Δ CRF level against the mean CRF level within each quintile. Floating variances were

used to calculate 95% confidence intervals for the HR in each group, including the reference group, to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (first quintile)[8]. For tests of interaction a bonferonni corrected P value of 0.01 was taken as significant. Two-sided analyses were performed using Stata version 13 (Stata Corp, College Station, TX, USA), and confidence intervals are presented at the 95% level.

Results

At baseline, the mean age of participants was 50.1 (6.5) years and mean baseline VO_2max was 33.1 (8.0) ml/min*kg; after 11 years, mean ΔVO_2max was -5.4 (5.4) ml/min*kg (**Table 1**). After a median follow-up duration of 14.3 (interquartile range: 13.3–15.1) years, 46 (9.6%) incident HF and 73 (15.2%) incident AF events were recorded, with a crude incidence rate of 7.3 (95% CI 5.5-9.8) per 1000 person-years for HF and 12.0 (95% CI 9.5-15.1) per 1000 person-years for AF respectively.

The relationship between ΔVO_2max and incident HF and AF is shown in **Figure 1**. **Table 2** shows the associations of ΔVO_2max with incident HF and AF events. In a multivariate analysis adjusted for age, baseline VO_2max, SBP, smoking status, history of type 2 diabetes and CVD, resting heart rate and left ventricular hypertrophy, 1 ml/min*kg higher ΔVO_2max was associated with a 10% relative risk reduction of HF, HR 0.90 (95% CI 0.83 to 0.97) which corresponds to a 31% relative risk reduction, 0.69 (95% CI 0.53 to 0.90) per 1 MET change in ΔVO_2max. The effect estimate was minimally attenuated on further adjustment for any death as a competing risk event, HR 0.93 (95% CI 0.86-0.99) per 1 ml/min*kg higher ΔVO_2max. HRs did not vary markedly by levels of pre-specified established risk factor (**Figure 2**).

Discussion

In this first ever population-based prospective study to examine the associations between directly measured change in CRF over time and risk of developing incident HF and AF, improvement in long-term fitness levels was associated with a significantly lower risk of HF in a graded fashion independent of known CVD risk factors, or death as a competing event. These findings were consistent in clinically relevant subgroups. Incident AF, however, was not related with the long term change in CRF levels seen across time points assessed.

These findings build upon prior work[9] where we have shown that long term improvement in CRF is associated with greater all-cause survival. Previously we reported that a 1 unit improvement in CRF is associated with 9% relative risk reduction for all-cause mortality[9] and here we show that a similar change, of 1 unit increase in CRF (as measured by maximal oxygen uptake, ml/kg/minute) was associated with a 10% reduced risk of incident HF events, corresponding to a 31% risk reduction of incident HF per 1-MET improvement in CRF.

The reduction in the risk of incident HF, with improvement in long term CRF may be a direct physiological effect of exercise and physical training on VO_2max or secondary to overall reduction in cardiovascular risk factors in individuals who were physically fit. However, these findings persisted even

after multivariate adjustment for CVD risk factors at baseline. Although residual confounding and time variate change in risk factors cannot be accounted for in our analysis, these results suggest that mechanisms other than simple cardiovascular risk factor reduction may account for health benefits associated with improved fitness. Regular exercise may increase the capacity of endothelial cells to evoke vasodilatation during early stages of atherosclerosis and thus retarding its progression [10,11]. Physical activity and fitness also has favorable effects, seen as improvements in cardiac output, left ventricular function, oxygen utilization, and the formation of collateral blood vessels[10,12,13]. It has been suggested that physical activity regulates cardiac autonomic function and vagal control of heart rate, therefore reducing risk of ventricular arrhythmias and subsequent risk of HF[14]. Evidence of additional benefits of improved fitness may be via anti-inflammatory pathways as increasing levels of CRF are associated with a reduction in levels of inflammatory markers like C-reactive protein[15,16]. In addition, improvement in CRF may also accompany modulation of markers of subclinical heart disease including natriuretic peptides and cardiac troponin T levels[17].

Although we did not observe any association with incident AF, this may be because CRF has a non-linear, almost J shaped association with AF as previously reported[7] and the small change in CRF observed in our analysis, may not significantly modulate the risk of incident AF to be detected in our analysis. Further work with longer duration of follow up, greater change in fitness levels and greater number of incident AF events may help ascertain any underlying association of AF with long-term change in fitness.

There are several strengths and limitations that merit consideration. The use of a prospective cohort design, complete follow-up, and detailed information on potential confounders were major strengths. As well as the direct measurement of CRF which prevented largely misclassification of exposure, that has been a limitation in previous studies of fitness and CVD outcomes, including HF and AF outcomes. We acknowledge that the study population, consisting of middle-age Finnish men only; limits generalization of our findings and these results need to be confirmed in other ethnic groups and in women. We acknowledge that only a subset of participants were randomly sampled at 11 years follow up for measurement of CRF and this may include a bias as only those who were alive at 11 years and able to perform cycle ergometer exercise tolerance test may have been sampled. We were unable to assess the differential impact of change in CRF on risk of HF with preserved versus reduced ejection fraction because there were no data on ventricular function post-HF development. Though many confounders were taken into account to ensure the validity of our results, there was a potential for residual confounding as with all observational studies. The diagnosis of AF was based on hospital discharge diagnosis, physician claims data base and study ECGs on follow up. This however may underestimate the diagnosis in particular paroxysmal AF events in study subjects who may be asymptomatic. In conclusion, the results of this study underline the importance of sustained CRF to reduce the risk of incident HF.

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The manuscript represents valid work and neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere. Data are available on request to the corresponding author.

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Conflict of interest

None

Ethics

The study was approved by the Research Ethics Committee of the University of Eastern Finland. Each participant gave written informed consent.

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FIGURE LEGENDS

Figure 1: Association between change in cardiorespiratory fitness and incident Heart failure and Atrial fibrillation

Figure 2: Change in cardiorespiratory fitness and incident Heart failure and Atrial fibrillation risk in subgroups.

Hazard ratios and 95% confidence intervals (CI) refer to a 1 unit increase in Δ cardiorespiratory fitness (1 ml/kg/min of maximal oxygen uptake). Hazard ratios are adjusted for age, baseline VO2max, smoking status, systolic blood pressure, cardiovascular disease, history of diabetes, heart rate, and left ventricular hypertrophy

Table1

Table 1: Baseline characteristics and cross-sectional correlates of ΔVO_{2max}.

Variable	Mean or %	SD or IQR	r or mean change (95% CI) relative to ref	P
Age (years)	50.1	6.5	0.09(0.01,0.16)	0.021
Systolic blood pressure (mmHg)	131.3	14.5	-0.00(-0.03,0.03)	0.957
Low-density lipoprotein cholesterol (mmol/L)	3.80	0.90	0.14(-0.40,0.68)	0.612
High-density lipoprotein cholesterol (mmol/L)	1.30	0.30	-1.87(-3.52,-0.21)	0.027
Creatinine (mg/L)[$]	1.01	0.92-1.11	0.24(-3.55,4.03))	0.900
Body mass index (kg/m2)[$]	26.3	24.4-28.7	0.13(-0.02,0.28)	0.079
Resting Heart Rate (beats/min)	62.1	10.5	0.06(0.02,0.11)	0.007
Smoking (yes)	23.1%	-	0.17(-0.99,1.32)	0.955
History of cardiovascular disease (yes)	27%	-	1.40(0.29,2.52)	0.013
History of type 2 diabetes mellitus (yes)	3.1%	-	-0.92(-3.71,1.87)	0.517
Left ventricular hypertrophy (yes)	0.4%		-1.08(-8.63,6.48)	0.780
VO_{2max} baseline (ml/min*kg)	33.1	8.0	-0.42(-0.48,-0.37)	<0.001
ΔVO_{2max} (ml/min*kg)	-5.4	5.4	-	-

SD: Standard deviation; **IQR**: Interquartile range; **CI**: Confidence Interval;
ΔVO_{2max}: VO_{2max} at 11 years - VO_{2max} at baseline

$ Data are reported as median [IQR] and correlation coefficients are estimated with logged transformed variable

Table2

Table 2 Association of change in cardiorespiratory fitness with incident heart failure and atrial fibrillation

ΔCRF ml/kg/min (mean)	Model 1	P	Model 2	**P**	**Model 3**	**P**
Heart Failure						
Q1	ref	ref	ref	ref	ref	ref
Q2	0.43 (0.20-0.92)	0.029	0.44 (0.20-0.96)	0.040	0.53 (0.24-1.15)	0.111
Q3	0.39 (0.18-0.87)	0.022	0.41 (0.18-0.91)	0.028	0.53 (0.22-1.24)	0.144
Per unit change	0.90 (0.84-0.97**)**	0.005	0.90 (0.83-0.97)	0.007	0.93 (0.86-0.99)	0.046
Per 1 MET change	0.69 (0.54-0.89)	0.005	0.69 (0.53-0.90)	0.007	0.76 (0.59-0.99)	0.046
Atrial Fibrillation						
Q1	ref	ref	ref	ref	ref	ref
Q2	0.70 (0.38-1.28)	0.249	0.68 (0.37-1.27**)**	0.230	0.76 (0.41-1.43)	0.395
Q3	0.87 (0.46-1.63	0.666	0.87 (0.46-1.64)	0.664	1.01 (0.53-1.93)	0.977
Per unit change	0.97 (0.92-1.02)	0.260	0.97 (0.92-1.02**)**	0.270	0.98 (0.93-1.03)	0.492
Per 1 MET change	0.89 (0.74-1.08)	0.260	0.89 (0.74-1.09)	0.270	0.94 (0.78-1.13)	0.492

CRF, cardiorespiratory fitness; Maximal oxygen uptake (ml/kg/min) was used as a measure of cardiorespiratory fitness; ref, reference
Model 1: Adjusted for age and baseline VO2max
Model 2: Model 1 plus systolic blood pressure, body mass index, history of cardiovascular disease, history of diabetes, smoking status, LVH, and resting heart rate
Model 3: plus any death as a competing risk
Note: 1 MET corresponds to 3.5 ml/kg/min change in VO2max

Figure1

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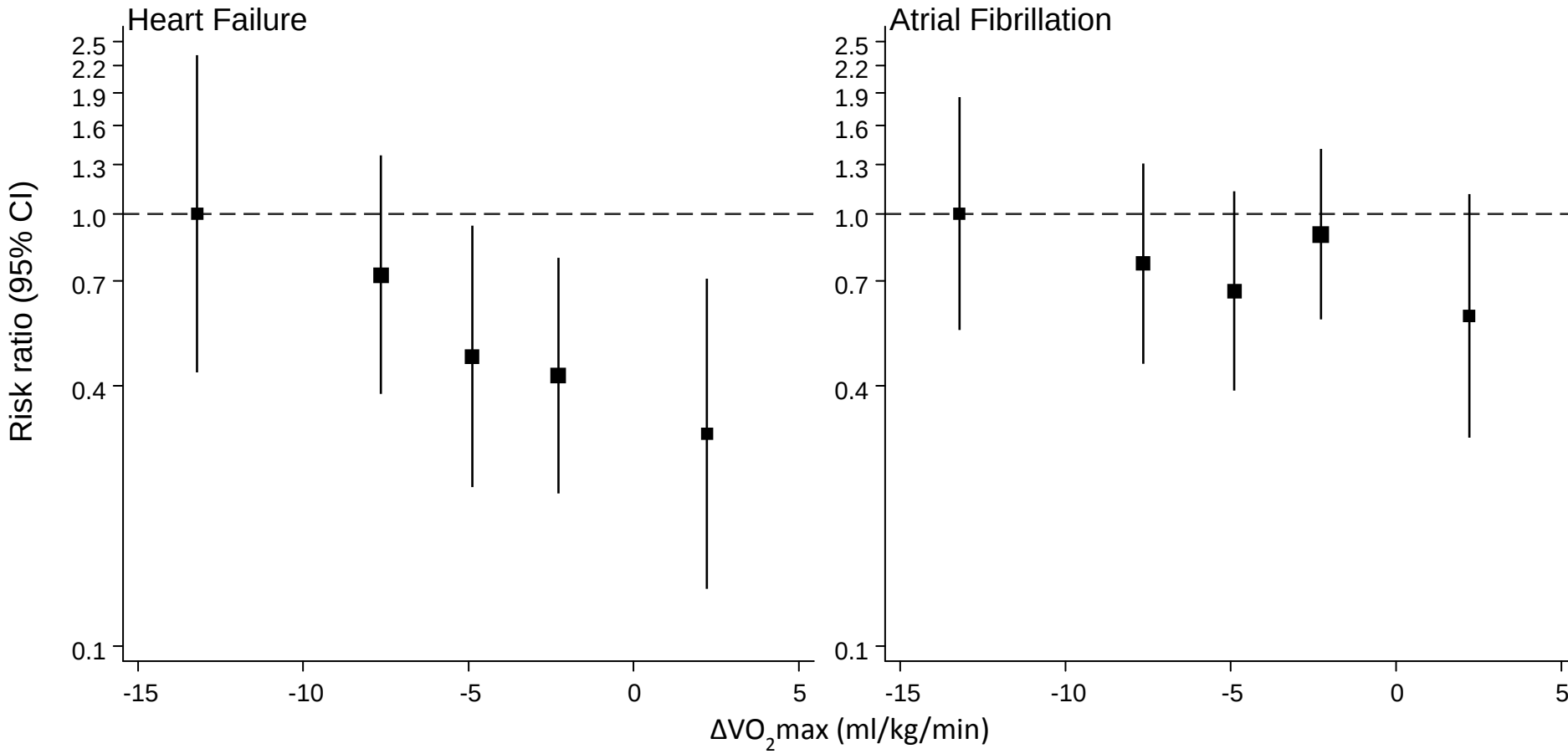
Figure 1



Hazard ratios were adjusted for age, baseline VO2max, smoking status, history of diabetes, history of cardiovascular disease, systolic blood pressure, left ventricular hypertrophy and heart rate. Hazard ratios (HR) were calculated in reference to the first quintile of Δ cardiorespiratory fitness (CRF), and plotted against the mean CRF within each category. 95% CIs were calculated from floating variances (including the reference group)

Figure2

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Figure 2