Graduate thesis

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Norwegian University of Science and Technology
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Graduate thesis in Medical school
Supervisor: Dalen, Håvard
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The Nord-Trøndelag Health Study

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Abstract

Purpose

To investigate the association between cardiorespiratory fitness (CRF) measured as peak oxygen uptake (VO_{2peak}) and different clinical, anthropometric, echocardiographic and leisure time physical activity measurements in patients with atrial fibrillation (AF). Identifying predictors of fitness in this population, can ease the selection of relevant factors in intervention studies. In addition, the new knowledge may add information on how to improve fitness in this group.

Methods

This cross-sectional study included data from the 4th wave of the Nord-Trøndelag Health Study (HUNT4), carried out in September 2017 to February 2019. 56 042 participants ≥20 years participated in HUNT4. If they (1) participated in HUNT3 Echocardiography sub-study, (2) HUNT3 Fitness Study, (3) had validated AF at the time of participation in HUNT3, or (4) had new onset self-reported AF by participation in HUNT4, they were invited to participate in Echocardiography and fitness sub-study (HUNT4 Heart Outcome Prediction Evaluation) (HUNT 4 HOPE). In addition to mentioned selection criteria, only participants who had participated in HUNT4 Echocardiography sub-study and had a respiratory exchange ratio ≥1 on VO_{2peak} treadmill testing were included in this study. Finally, 564 participants with validated or self-reported AF, and 1754 participants with sinus rhythm, were included. All participants went through biochemical and clinical measurements, and were examined with echocardiography and VO2 max treadmill testing by our group. In addition, data of self-reported physical activity, medications and disease status were sampled through the HUNT studies.

Statistical analysis

Descriptive statistics of continuous variables with normal distribution is presented as means ± standard deviations (SD). Categorical variables are presented as frequencies (N) and percentages (%). Group-level comparison is done with Independent Samples T-Test for independent samples. Pearsons Chi square and Fisher's Exact Test (sample size ≤5) are used to compare proportions (observed vs expected proportions). Associations were studied with univariate and multivariable logistic regression analysis, and such approach was used to identify predictors of estimated cardiorespiratory fitness in the study population.

Results

The predictors strongest associated with fitness were age, sex, percent body fat, resting heart rate, left ventricular end-diastolic volume, left ventricular ejection fraction and inactivity. Together the seven predictors explained 72.3% of the variation in $VO_{2\ peak.}$ With a p-value of

<0.001, non-AF participants had a greater mean $VO_{2\ peak}$ than AF participants, equivalent to 2mL/kg/min. This difference could not be addressed to any of the seven predictors, as there was no statistical difference between groups, indicating that verified atrial fibrillation had an influence on fitness.

Conclusions

Seven important predictors of fitness account for >70% of the variability in $VO_{2\ peak}$ in the HUNT 4 HOPE Study, and the results were similar in AF patients and individuals in sinus rhythm. These results support that AF participants can be treated the same as non-AF participants in supervision to improve fitness.

INTRODUCTION

With a prevalence of 1-2% in the general population, atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance. Recent evidence suggests a rising prevalence and incidence worldwide.[1, 2] These changes may in part be explained by the aging trends in the global population, as the prevalence of AF increases with advancing age, but an increase in AF incidence are also demonstrated in studies after age adjustments.[2] This is probably a reflection of lifestyle changes, comorbidity and cardiovascular risk factors.[2]

Several risk factors are known to be independent predictors and/or contributors to AF development. Aging, male sex, hypertension, heart failure, coronary artery disease, myocardial infarction, abnormal heart valves, left ventricular hypertrophy, increased pulse pressure (measure of aortic stiffness), diabetes, obesity, metabolic syndrome, obstructive sleep apnea, lung disease, hypo-/hyperthyroidism, exposure to stimulants such as tobacco or alcohol, physical inactivity, poor cardiorespiratory fitness and excessive high-intensity endurance training are all risk factors of AF development.[3, 4] Some people develop AF without identifiable risk factors or comorbidities, called lone atrial fibrillation.[3] This demonstrates the heterogeneity in the AF population.

Patients with AF are at increased risk of death, heart failure, hospitalization and thromboembolic events.[5] They also have poorer quality of life (QoL) compared to both healthy controls, the general population, and patients with coronary heart disease.[6] As AF is already known to have a significant impact on healthcare costs, a rising prevalence and incidence will result in further increased healthcare use and cost in the future.[3] This highlights the needs of new strategies to both lower the probability of developing AF and prevent disease progression in already affected individuals to improve their health outcomes.

Today’s treatment options include anticoagulation therapy, frequency- and rhythm control and invasive catheter ablation technology. The insufficiency of these treatment options has led to increased focus on lifestyle and risk factor modification as non-invasive treatment strategies. Recent research has demonstrated significant associations between such strategies and sinus rhythm maintenance or reduced AF burden through, among others, improved QoL and cardiorespiratory fitness.[3] In general, CRF is considered a reflection of total body health.[7]

In individuals with atrial fibrillation, physical activity and higher levels of eCRF are associated with lower risk of all-cause mortality and cardiovascular disease (CVD) mortality and morbidity.[8, 9] A recent study indicates lower rates of major adverse events after 1-year follow up among AF patients reporting regular or intense physical activity compared with no activity.[8]

This supports the importance of regular physical activity and improved CRF in AF patients. Yet, there is a lack of exercise recommendations for AF patients, and little is known about fitness in this population. Identifying what characterizes CRF in this group, will ease the selection of relevant factors in intervention studies.

In this study, our group has quantified the participants CRF through peak oxygen uptake (VO_{2peak}) measured by treadmill test (direct measurement, gas exchange). The goal was to identify the strongest predictors associated with fitness in AF participants, and to investigate if these predictors were different between AF and non-AF participants.

METHODS

Study population and study design

This study included data from the 4th wave of the Nord-Trøndelag Health Study (HUNT4), carried out in September 2017 to February 2019. HUNT is a large population-based cohort study in the northern region of Trøndelag County, Norway. Further details about the total cohort profile have been described for HUNT 3, and are published elsewhere.[10] Out of 103 782 invited to participate in HUNT4, a total of 56 042 (54%) adult women and men ≥20 years responded. If they (1) participated in HUNT3 Echocardiography sub-study, (2) HUNT3 Fitness Study, (3) had validated AF at the time of participation in HUNT3, or (4) had new onset self-reported AF by participation in HUNT4, they were invited to participate in Echocardiography and fitness sub-study (HUNT4 Heart Outcome Prediction Evaluation) (HUNT 4 HOPE). This resulted in 273 participants with a validated AF diagnosis from HUNT3, 427 participants with self-reported AF from HUNT 4 (validations process is ongoing), 1581 participants from HUNT3 Fitness Study and 544 participants from HUNT3 Echocardiography sub-study. The validation process of AF diagnoses in this cohort is previously described in detail.[11] In addition to mentioned selection criteria, only participants who had participated in HUNT4 Echocardiography sub-study and had a respiratory exchange ratio ≥1 on VO_{2peak} treadmill testing, were included in this study. Finally, 564 participants with validated or self-reported AF, and 1754 participants without AF were included.

HUNT3 Fitness Study was designed to obtain measures of VO_{2max} in a healthy population and was conducted between June 2007 and June 2008. To enter the VO_{2max} testing, participants had to be free from cancer, cerebral and cardiovascular disease, respiratory disease and sarcoidosis in HUNT3 Questionnaire 1. In addition, they should not be using drugs for elevated blood pressure, and they had to pass a brief medical interview. Exclusion criteria for the HUNT4 fitness study were uncontrolled high blood pressure (>180/100 mm Hg), recent heart failure admission (<6 weeks), unstable angina, serious cardiac arrhythmia, pulmonary hypertension, recent deep venous thrombosis or pulmonary embolus, symptomatic valvular or other serious heart disease including pacemaker or implantable cardioverter defibrillator, recent acute myocardial infarction (last 4 weeks), active cancer treatment (last 4 weeks), chronic or acute contagious infectious disease, diagnosed dementia, pregnancy, or restrictions to physical activity ordered by a physician.

All attending participants have filled in a self-report questionnaire, been through clinical and biochemical measurements, and were examined with cardiovascular ultrasound and oxygen uptake. Also, all participants have agreed through HUNT in general and our project to this form of data use. The study is approved by the regional committee for medical and health research ethics (REK) (the Echo-part; REK 2018/2416 and Fitness-part; REK 7243).

Questionnaire-based information
All participants in HUNT4 received an invitation letter by post which included a self-report questionnaire (Q1) and an information pamphlet. Q1 was filled in at home, and the participants delivered Q1 and the written consent when they attended the basic health examination sites.

Participants medical history, and other self-reported data, were collected through Q1, and through interviews done by attendance HUNT 4 HOPE. Self-reported data included information on disease status (Do you have, or have you had, any of the following diseases? Answer options 'yes' or 'no') and medications, leisure-time physical activity (LTPA), smoking and alcohol habits. Diseases included in this study were myocardial infarction, heart failure, stroke/brain haemorrhage, diabetes, hypothyroidism, hyperthyroidism, angina pectoris and kidney disease (except urinary tract infection).

Smoking status was mapped through five smoking variables ("never smoked", "I have previously smoked occasionally", "I have previously smoked daily", "I currently smoke occasionally", "I currently smoke daily"), and was dichotomized to "smoke today/smoked earlier" and "never smoked". Alcohol intake was mapped through the question "about how often during the last 12 months did you drink alcohol (do not include low-alcoholic beer)", with answer-options "never drunk alcohol", "not at all the last year", "once a month or less", "2-4 times a month", "2-3 times a week", "4 times or more a week". The alcohol variable was dichotomized to "< 2-3 times a week" and "≥ 2-3 times a week".

Clinical and biochemical measurements
Detailed information on collection of these measures have been described for HUNT3 [10], and the measures were done at the HUNT4 main test station. Briefly, clinical examinations and anthropometry included standardized measurement of weight wearing light clothes without shoes, height standing relaxed, and waist circumference horizontally at umbilical level in a relaxed standing position with arms hanging. Other clinical measurements included are body mass index (BMI), percent body fat and level of visceral fat measured by InBody770 (InBody Europe, Amsterdam, the Netherlands) based on bioelectrical impedance measurements, blood pressure (BP) and resting heart rate (RHR) measured using Dinamap CARESCAPE V100 (GE Healthcare) with GE TruSignal for pulse oximetry. Blood pressure (diastolic and systolic) is a rounded arithmetic mean of measurement 2 and 3, if all three were available. The last measurement was used if only two measurements were available. Biochemical measurements included non-fasting blood samples of high-density lipoprotein (HDL) and total cholesterol, creatinine, c-reactive protein and glycosylated haemoglobin (HbA1c).

Leisure-time physical activity
Participants' fitness data was collected through questionnaire-based information about their leisure-time physical activity (LTPA), and through directly measured peak oxygen uptake (VO_{2peak}) by treadmill test. Information on LTPA was gathered by validated questionnaires in the baseline examinations of HUNT4.[12, 13] By exercise we mean going for walks, skiing, swimming and working out/sports. The questionnaire contained three items on physical activity including frequency, intensity and duration. Question 1: "How frequently do you exercise" (never [0], less than once a week [0], once a week [1], 2-3 times a week [2.5] or nearly every day [5]), question 2[*]: "If you exercise as frequently as once or more times a week, how hard do you push yourself?" ("I take it easy, I don't get out of breath or break a sweat" (low), "I push myself until I'm out of breath and break into a sweat" (moderate), or "I practically exhaust myself" (high)), and question 3[*]: "How long does each session last?" (Less than 15 minutes [7.5], 15-29 minutes [22.5], 30-60 minutes [45] or more than 1 hour [75]). Weekly minutes of

LTPA was calculated based on values in brackets multiplied with weighted intensity (low [0.5], moderate [1], high [2]). Adherence to LTPA recommendations[14] was defined as ≥ 75 minutes of high intensity LTPA, ≥ 150 minutes of moderate intensity LTPA or ≥ 300 minutes of low intensity LTPA.

*Participants' answers were deleted from question 2 and 3 if they reported "never" or "less than once a week" on question 1 ("how often do you exercise"), as this was interpreted as inactive, and yielded an index score of zero.

VO_{2peak} measurements
The protocol used in cardiopulmonary exercise testing has been described previously.[15]
In short, an individualized protocol was applied to measure VO_{2max} using mixing chamber gas-analyser ergospirometry (Cortex MetaMax II, Cortex, Leipzig, Germany). Each participant did a 10-minute warm-up, and the test was initiated from the inclination and speed derived from warm up with the participants wearing a tight face mask (Hans Rudoplh, Germany) connected to the MetaMax II. When the participant reached an oxygen consumption that was stable for 30 seconds, inclination (1-2% each step) or velocity (0.5-1 km•h^{-1}) on the treadmill was increased until exhaustion. As 12.6% of the participants did not achieve VO_{2max} the term VO_{2peak} was used. Participants were excluded from this study if they had a respiratory exchange ratio <1.0, indicating a submaximal effort, supported by previous studies.[16] VO_{2peak} construction: VO (volume oxygen) x 1000/weight.

Echocardiography
All examinations and analyses were conducted by one of two sonographers (KS and EOJ), both experienced in advanced echocardiography. Examinations were performed in the left lateral decubitus position with a Vivid E95 scanner (GE Ultrasound, Horten, Norway) using a 3.5 Mhz phased-array transducer with options for 3D imaging (4VC). All analysis was performed in EchoPAC SWO 203 (GE Ultrasound).

Left ventricular internal dimension and right ventricular basal diameter were measured at end-diastole in parasternal long-axis and dedicated four-chamber views, respectively. Left ventricular end-diastolic volume (LV EDV), estimation of left ventricular ejection fraction (EF) and left and right atrial end-systolic (maximal) volumes were assessed in two-dimensional (2D) and three-dimensional (3D) (exception right atrial volume by 2D only) grey scale recordings. Volumes were not adjusted for body surface area in this study. In 2D the left ventricular endocardial border was traced at end-diastole and end-systole in four- and two chamber view, and similarly left atrial endocardial border was traced in dedicated four- and two-chamber views at end-systole. The right atrial volume was measured similarly, but in dedicated four-chamber view only. Volumes and EF were calculated by the methods of disc summation. 3D calculations were performed semi-automatically by the LVQ and LAQ packages in EchoPAC. The tracings of the endocardial borders were done at the discretion of the operator when necessary. Mitral inflow peak early diastolic velocity (E) was assessed by pulsed wave Doppler. Mitral annular peak longitudinal velocities were assessed from the septal and lateral wall by pulsed wave tissue Doppler for peak systolic (S') and peak early diastolic velocities (e'). A surrogate for LV filling pressure was calculated by the ratio of the early mitral inflow to the early diastolic mitral annular velocity (E/e') using an average of the septal and lateral e'. Tricuspid Annular Plane Systolic Excursion (TAPSE) was measured in reconstructed motion mode (M-mode) and serves as a parameter of global right ventricular function.

Valvular functions were assessed semi-quantitatively according to current recommendations.[17-19] Due to low prevalence of valvular diseases (see table 5), a composite including the eight variables at least moderate aortic-, mitral-, tricuspid- and/or pulmonic stenosis and/or regurgitation was made.

Statistical analysis

All analyses were performed using IBM SPSS (Statistical Product and Service Solutions) Statistics, version 26. Descriptive statistics of continuous variables with normal distribution is presented as means ± standard deviations (SD). Categorical variables are presented as frequencies (N) and percentages (%).

Group-level comparison is done with Student's t-test for independent samples. Pearsons Chi square and Fisher's Exact Test (sample size ≤ 5) are used to test proportions (observed vs expected proportions).

Associations were studied with univariate and multivariate regression analyses and were used to identify predictors of estimated cardiorespiratory fitness in the study population. The analyses were performed for AF- and non-AF participants individually. Statistical significance is assessed by P-value of <0.05. At first, univariate analysis was used to test one individual variable at a time. The variables with the highest level of significance and R squared, were included in multivariable analysis. In step one (multivariable analysis), we adjusted for age and gender for both groups to evaluate which one of the variables were more important. The strongest predictors of VO_{2peak} were the same for both groups, and the seven strongest predictors identified in step 1, were included in step 2. In step 2, all seven variables were included in the same equation to see what proportion of the relationship they explained together. We also tested if there was a mean difference in $VO_{2\,peak}$ between AF and non-AF participants after adjusting for the seven most important variables.

In univariate analysis, all body measurements (waist circumference, percent body fat, level of visceral fat and body mass index (BMI)) came out highly significant for both groups, and they were all a strong predictor of VO_{2peak}. Since they explained nearly the same variance in $VO_{2peak,}$ also after adjusting for age and sex, we included only percent body fat in the final equation.

RESULTS

Study population and descriptive data

In total, 3528 adult men and women in Nord-Trøndelag county participated in HUNT 4 HOPE. After excluding participants with either missing data or submaximal effort on VO_{2peak} treadmill testing, 2318 participants were included in this study. Among 564 (25%) participants with a verified atrial fibrillation diagnosis, 200 (35.5%) were women and 364 (64.5%) men. The respective values for non-AF participants were 1754 (75%), 916 (52.2%) women and 838 (47.8%) men.

Baseline clinical and laboratory findings from screening of the 2318 participants are presented in table 1, according to sex and AF status. Men were on average 1.5 years older than women, and there was an age difference between groups corresponding to AF participants being 5 years older. For most of the variables, there was a statistical difference between AF and non-AF participants. These differences were seen both when comparing within sexes, and for comparisons between groups based on AF-status.

AF participants scored higher than non-AF on all body measurements (weight, body mass index, percent body fat, level of visceral fat and waist circumference) when comparing same sex. On average, AF participants had a one unit higher BMI than non-AF participants. Systolic blood pressure was also slightly higher among AF- compared to non-AF participants, even though 34.2% of the AF participants and 12.2% of the non-AF participants were on blood pressure medication.

The occurrence of self-reported cardiac and cerebrovascular comorbidities was higher in AF participants in general, ranging between 5.5-8.3%, and when comparing within sexes. Myocardial infarction was 3.5 times more frequent in AF participants. The corresponding ratios for heart failure, stroke and angina pectoris were 12.2, 6.4 and 5.5, respectively.

Occurrence of diabetes were higher in AF men, than non-AF men with prevalence 8.6% and 3.6%. In women, there was no statistical difference. Also, kidney disease and hypothyroidism were more frequent among AF-participants. No difference was seen in the occurrence of hyperthyroidism.

There was no difference between groups in alcohol habits, but more AF- than non-AF participants were smokers (ex-smokers (53.4% vs 43.4%) and current smokers (5.3% vs 4.4%)).

Table 1. Baseline clinical characteristics of the study population

	Women			Men			All		
Variable	AF	non-AF	p-value	AF	non-AF	p-value	AF	non-AF	p-value
n	199	912		365	835		564	1747	
Age (years)	63.3 (13.4)	58.6 (12.2)	<0.001	65.0 (12.2)	60.0 (12.1)	<0.001	64.4 (12.6)	59.2 (12.2)	<0.001
Weight (kg)	72.6 (12.4)	70.0 (11.5)	<0.001	87.9 (12.3)	85.2 (11.7)	.001	82.5 (14.3)	77.3 (13.9)	<0.001
Height (cm)	166 (6)	166 (6)	.703	180 (6)	179 (6)	.340	175 (9)	172 (9)	<0.001
BMI (kg/m2)	26.5 (4.7)	25.5 (3.9)	.004	27.2 (3.5)	26.5 (3.3)	.001	27.0 (4.0)	26.0 (3.7)	<0.001
Weight class			.004			.017			<0.001
- BMI < 25*	80 (40.0)	471 (51.5)		107 (29.2)	277 (33.1)		33.0 %	42.7%	
- BMI 25 – 29.9*	81 (40.5)	327 (35.8)		192 (52.5)	457 (54.7)		48.2%	44.8%	
- BMI ≥ 30*	39 (19.5)	116 (12.7)		67 (18.3)	102 (12.2)		18.7%	12.5%	
Percent body fat	34.4 (8.2)	32.5 (7.7)	.002	25.3 86.7)	23.5 (6.4)	<0.001	28.5 (8.4)	28.2 (8.4)	.453
Level of visceral fat	12.3 (5.4)	10.9 (4.9)	<0.001	10.4 (4.2)	9.1 (3.7)	<0.001	11.1 (4.7)	10.0 (4.5)	<0.001
Waist circumference (cm)	93 (13)	90 (12)	.001	99 (12)	96 (11)	<0.001	97 (13.0)	93 (12)	<0.001
Systolic BP (mmHg)	132 (19)	128 (19)	.002	135 (18)	132 (17)	.004	134 (18)	130 (18)	<0.001
Diastolic BP (mmHg)	73.4 (10.2)	72.6 (8.8)	.291	79.0 (10.5)	78.2 (9.6)	.203	77.0 (10.7)	75.3 (9.6)	.001
Resting HR (beats/min)	70.4 (12.9)	70.0 (11.2)	.771	69.0 (14.0)	66.6 (11.7)	.005	69.4 (13.6)	68.4 (11.5)	.105
HDL cholesterol (mmol/L)	1.60 (0.39)	1.63 (0.37)	.347	1.28 (0.32)	1.32 (0.31)	.069	1.39 (0.38)	1.48 (0.38)	<0.001
Cholesterol (mmol/L)	5.43 (1.03)	5.69 (1.06)	.001	5.02 (1.09)	5.44 (1.05)	<0.001	5.17 (1.09)	5.58 (1.06)	<0.001
Creatinine (µmol/L)	70.4 (14.3)	66.9 (10.0)	.001	86.1 (17.5)	82.0 (13.0)	<0.001	80.5 (18)	74.1 (13.7)	<0.001
CRP (mg/L)	2.35 (5.78)	1.97 (4.11)	.284	2.04 (3.24)	1.65 (2.43)	.022	2.15 (4.31)	1.82 (3.41)	.063
HbA1c (mmol/mol)	34.6 (4.8)	33.5 (3.7)	.002	35.8 (6.1)	5.26 (5.3)	.002	35.4 (5.7)	34.0 (4.5)	<0.001
Myocardial infarction*	6 (3.3)	2 (0.2)	<0.001	26 (7.4)	28 (3.4)	.002	32 (6)	30 (1.7)	<0.001
Heart failure*	4 (2.2)	2 (0.2)	.009	28 (8.1)	6 (0.7)	<0.001	32 (6.1)	8 (0.5)	<0.001
Stroke/brain haemorrhage*	9 (4.9)	9 (1.0)	<0.001	35 (10)	13 (1.6)	<0.001	44 (8.3)	22 (1.3)	<0.001
Diabetes*	5 (2.5)	16 (1.8)	.562	31 (8.6)	30 (3.6)	<0.001	36 (6.4)	46 (2.6)	<0.001

Hypothyroidism[*]	30 (16.3)	89 (10)	.013	19 (5.4)	21 (2.5)	.013	49 (9.1)	110 (6.4)	.031
Hyperthyroidism[*]	6 (3.3)	21 (2.4)	.483	6 (1.7)	4 (0.5)	.073	12 (2.3)	25 (1.5)	.207
Angina pectoris[*]	7 (3.9)	3 (0.3)	<0.001	22 (6.3)	15 (1.8)	<0.001	29 (5.5)	18 (1.0)	<0.001
Kidney disease[1*]	13 (7)	15 (1.7)	<0.001	18 (5.1)	15 (1.8)	.002	31 (5.7)	30 (1.7)	<0.001
BP-medication today?[*]	57 (28.4)	87 (9.5)	<0.001	137 (37.4)	127 (15.2)	<0.001	194 (34.2)	214 (12.2)	<0.001
Alcohol[3*]	78.2/21.8	73.4/26.6	.381	63.6/36.4	65.6/34.4	.051	68.7/31.3	69.7/30.3	.190
Smoke[2]	6.0/56.2	5.1/44.4	.005	4.9/51.9	3.6/42.4	.002	5.3/53.4	4.4/43.4	<0.001

Values are presented as mean (SD) or as n (%)[*]. Abbreviations: SD = standard deviation; BMI = body mass index; BP = blood pressure; HR = heart rate; HDL-cholesterol = high-density lipoprotein cholesterol; CRP = c-reactive protein; HbA1c = glycosylated haemoglobin;
[1]Expect urinary tract infection, [2]Smoke: smoke today/smoked earlier, [3]Alcohol: less than 2-3 days a week/ ≥ 2-3 days a week.

Fitness
Table 2 shows mean VO_{2peak} indices among the study participants, stratified by sex and AF-status. Participants with a respiratory exchange ratio <1 were excluded, indicating a submaximal effort. AF women had an overall mean VO_{2peak} of 28.9±7.4 $mL \cdot kg \cdot min^{-1}$, while the respective numbers for men were 34.7±9.8. Non-AF participants scored consistently higher than AF participants with approximately five units. P-value <0.001 for all variables except ventilation (L/min) between AF and non-AF participants as a group (p-value: .006).

Table 2. $VO_{2\ peak}$ measurements

	Women		Men		All	
Variable	**AF**	**non-AF**	**AF**	**non-AF**	**AF**	**non-AF**
n	201	916	367	838	568	1754
Ventilation (L/min)	72.9 (16.7)	80.4 (16.8)	109 (25)	122 (24)	96 (28)	100 (29)
Absolute VO2 (L/min)	2.07 (0.47)	2.33 (0.49)	3.01 (0.83)	3.42 (0.78)	2.68 (0.85)	2.85 (0.84)
Relative VO2peak (ml/kg/min)	28.9 (7.4)	33.6 (7.6)	34.7 (9.8)	40.4 (9.2)	32.6 (9.4)	36.9 (9.0)

Values are presented as mean (SD), except for n which is given as numbers. Abbreviations: VO_{2peak} = peak oxygen uptake.

Leisure time physical activity
Adherence to recommendations and weighted LTPA minutes are presented in table 3. More non-AF than AF women were adherent to recommendations, and less non-AF women were inactive. No differences were seen between men with and without AF, respectively. Weighted LTPA minutes showed no difference between any of the groups.

Table 3. Leisure time physical activity (LTPA).

	Women			Men			All		
	AF	non-AF	p-value	AF	non-AF	p-value	AF	non-AF	p-value
Adherence recommendations[1]	54 (27.0)	314 (34.3)	.047	108 (29.7)	264 (31.5)	.528	162 (28.7)	578 (33.0)	.061
Inactive[2]	19 (9.6)	37 (4.1)	.001	28 (7.8)	57 (6.9)	.575	47 (8.4)	94 (5.4)	.010
Low intensity			.523			.808			.420
1-75 minutes	34 (17.0)	126 (13.8)		59 (16.2)	125 (14.9)		93 (16.5)	251 (14.3)	
75-150 minutes	8 (4.0)	45 (4.9)		13 (3.6)	39 (4.7)		21 (3.7)	84 (4.8)	
> 150 minutes	2 (1.0)	17 (1.9)		5 (1.4)	11 (1.3)		7 (1.2)	28 (1.6)	
Moderate intensity			.409			.814			.600
1-75 minutes	17 (8.5)	77 (8.4)		35 (9.6)	67 (8)		52 (9.2)	144 (8.2)	
75-150 minutes	51 (25.5)	195 (21.3)		83 (22.8)	200 (23.9)		134 (23.8)	395 (22.5)	
> 150 minutes	46 (23.0)	257 (28.1)		92 (25.3)	217 (25.9)		138 (24.5)	474 (27.0)	
High intensity			.324			.506			.123
1-75 minutes	0	0		0	0		0	0	
75-150 minutes	0	10 (1.1)		0	1 (0.1)		0	11 (0.6)	
> 150 minutes	6 (3.0)	30 (3.3)		11 (3.0)	35 (4.2)		17 (3.0)	65 (3.7)	

Data are presented as n (%). Abbreviations: LTPA = leisure time physical activity. [1]Adherence to weekly LTPA recommendations, [2]Exercise never or less than once a week.

Echocardiography
Table 4 displays echocardiographic indices of the study population. The reliability of most of the measurements have been described previously by our group,[20] and in ongoing studies (data not available) the variability in the presented population will be evaluated.

Most of the variables were different between AF and non-AF participants. As expected, left atrium (LA) was enlarged in AF participants, and significantly larger than in the non-AF group. AF participants had a mean LA end-systolic volume of 71.0ml ± 28.3ml (women; 55.9±15.3, men 79.8±30.3). Respective volumes for non-AF women and men were 4 ml and 17 ml less. Mean right atrium end-systolic volume was also greater in AF men (62.6ml ± 33.0) than in non-AF men with a difference of 11 ml. No difference was seen between women.

With respect to left ventricular end-diastolic volume (LV EDV) there was no difference between AF and non-AF participants in either 2D or 3D measurements, except 2D measurements in women (p-value .044). Mean LV EDV 3D were approximately 100 ml for women, and 133 ml for men. Left ventricular ejection fraction (LV EF) differed between groups. Mean LV EF was 58.9% in AF women and 55.8% in AF men. The respective numbers for non-AF participants were 1.1 and 2.4 percentage point higher.

Table 4. Echocardiographic indices of the study population

	Women			Men			All		
Variable	**AF**	**non-AF**	**p-value**	**AF**	**non-AF**	**p-value**	**AF**	**non-AF**	**p-value**
Mean n	172	781		310	735		482	1516	
LV EDV (2D) (ml)	92 (23)	94 (22)	.130	125 (36)	127 (29)	.330	113 (36)	110 (31)	.127
LV EDV (3D) (ml)	98 (23)	102 (22)	.044	132 (34)	134 (28)	.525	120 (35)	118 (29)	.162
LV EF (2D) (%)	59.2 (6.9)	60.4 (4.9)	.039	56.9 (8.4)	59.4 (5.7)	<0.001	57.8 (8.0)	59.9 (5.4)	<0.001
LV EF (3D) (%)	58.9 (6.3)	60.0 (4.8)	.039	55.8 (7.4)	58.2 (4.8)	<0.001	56.9 (7.2)	59.1 (4.9)	<0.001
Mitral annular S' (cm/s)	7.7 (1.6)	8.3 (1.6)	<0.001	7.9 (2.09)	8.9 (1.77)	<0.001	7.8 (1.9)	8.6 (1.7)	<0.001
Mitral annular e' (cm/s)	8.9 (2.8)	9.4 (2.9)	.027	9.1 (2.6)	9.0 (2.7)	.733	9.0 (2.7)	9.2 (2.8)	.149
Mitral E/e' ratio (cm/s)	9.0 (2.8)	8.2 (2.3)	<0.001	8.4 (2.8)	7.7 (2.0)	<0.001	8.6 (2.8)	8.0 (2.2)	<0.001
TAPSE (cm)	2.33 (0.49)	2.38 (0.46)	.119	2.29 (0.56)	2.47 (0.50)	<0.001	2.30 (0.53)	2.42 (0.48)	<0.001
LA ESV (2D) (ml)	56.5 (21.2)	49.7 (15.8)	<0.001	82.0 (35.8)	62.6 (20.8)	<0.001	72.7 (33.6)	55.8 (19.4)	<0.001
LA ESV (3D) (ml)	55.9 (15.3)	51.9 (21.2)	.005	79.8 (30.3)	62.7 (16.1)	<0.001	71.0 (28.3)	57.1 (15.3)	<0.001
RA ESV Ch4 (ml)	37.0 (17.9)	34.9 (12.3)	.168	62.6 (33.0)	51.5 (20.7)	<0.001	54.0 (31.2)	43.1 (18.9)	<0.001
LV ED InDi (mm)	46.2 (5.5)	46.9 (4.9)	.115	52.1 (6.1)	50.9 (5.5)	.002	50.0 (6.5)	48.8 (5.6)	<0.001
RV ED BasDm (cm)	3.28 (0.52)	3.28 (0.53)	.939	3.99 (0.74)	3.89 (0.66	.051	3.76 (0.75)	3.58 (0.67)	<0.001
Valvular disease[1*]	14 (7.0)	16 (1.8)	<0.001	31 (8.8)	15 (1.8)	<0.001	45 (8.2)	31 (1.8)	<0.001

Values are presented as mean (SD) and n (%)[*]. Abbreviations: LV EDV = left ventricular end-diastolic volume; EF = ejection fraction; Mitral annular S' = mean of peak systolic mitral annular septal- and lateral wall; Mitral annular e' = mean of peak early diastolic mitral annular septal- and lateral wall; Mitral E/e' ratio = mitral inflow peak early diastolic velocity to Mitral annular e' ratio; TAPSE = tricuspid annular plane systolic excursion; LA ESV = left atrium end-systolic volume; Ch4 = 4-chamber view; LV ED InDi = left ventricular end-diastolic internal dimension; RV ED BasDm = right ventricular end-diastolic basal diameter. [1]Valvular disease: ≥moderate valvular disease.

Table 5 shows the distribution of moderate or more severe valvular disease among AF and non-AF participants. Overall, the prevalence was higher for AF than non-AF participants, with aortic valve stenosis (AF; 3.9%, non-AF; 1.4%) and mitral valve regurgitation (AF; 3.8%, non-AF; 0.17%) as the most common valvular pathology.

Table 5. Moderate or severe valvular disease

	All	
Variable	**AF**	**Non-AF**
Aortic valve stenosis	19 (3.5%)	20 (1.2%)
Mitral valve stenosis	1 (0.2%)	1 (0.06%)
Tricuspid valve stenosis	0	1 (0.06%)
Pulmonic valve stenosis	0	1 (0.06%)
Aortic valve regurgitation	11 (2.1%)	8 (0.5%)
Mitral valve regurgitation	13 (2.4%)	2 (0.1%)
Tricuspid valve regurgitation	9 (1.6%)	2 (0.1%)
Pulmonic valve regurgitation	0	0

Values are presented as n (%).

Table 6 shows the association of different independent variables with change in relative peak oxygen uptake (VO_{2peak}, mL/kg/min) (dependent variable). The table indicate what predicts fitness for both groups, before adjusting for any of the individual variables.

When analysing univariate associations with VO_{2peak} as the dependent variable, VO_{2peak} was most strongly associated with different body measurements as percent body fat and BMI, resting heart rate, use of blood pressure medication, echo indices as left ventricular end diastolic volume and ejection fraction, and inactivity. The same independent variables were significantly associated with VO_{2peak} in the AF and non-AF group. Based on the individual R^2 values (estimating how much of the variance in VO_{2peak} that could be explained by each of the variables) and the level of significance, the strongest variables were included in multivariable regression analysis (table 7).

Table 6. Linear regression analyses with VO2-peak as the dependent variable

	AF			Non-AF		
Independent variables	**β-coefficient**	**R^2**	**p-value**	**β-coefficient**	**R^2**	**p-value**
Sex (men)	5.706	.084	<0.001	6.836	.145	<0.001
Age (years)	-.447	.359	<0.001	-.429	.333	<0.001
Weight (kg)	-.071	.012	.010	-.030	.002	.055
Height (cm)	.337	.103	<0.001	.361	.128	<0.001
BMI (kg/m2)	-.850	.128	<0.001	-.812	.108	<0.001
Percent body fat	-.721	.419	<0.001	-.747	.481	<0.001
Level of visceral fat	-1.186	.359	<0.001	-1.265	.389	<0.001
Waist circumference (cm)	-.264	.131	<0.001	-.288	.141	<0.001
Systolic BP (mmHg)	-.107	.043	<0.001	-.131	.067	<0.001

Diastolic BP (mmHg)	.021	.001	.576	.012	.000	.591
Resting HR (beats/min)	-.176	.065	<0.001	-.236	.090	<0.001
HDL cholesterol (mmol/L)	1.560	.004	.137	-.996	.002	.082
Cholesterol (mmol/L)	.844	.010	.020	-1.356	.025	<0.001
Creatinine (µmol/L)	-.070	.018	.001	.088	.018	<0.001
CRP (mg/L)	-.307	.020	.001	-.417	.025	<0.001
HbA1c (mmol/mol)	-.399	.058	<0.001	-.543	.074	<0.001
Myocardial infarction	-5.351	.019	.002	-3.579	.003	.031
Heart failure	-5.236	.018	.002	-5.263	.002	.101
Stroke/brain haemorrhage	-4.411	.017	.003	-6.998	.008	<0.001
Diabetes	-2.754	.005	.091	-8.035	.020	<0.001
Hypothyroidism	-2.081	.004	.138	-4.896	.018	<0.001
Hyperthyroidism	.027	.000	.992	-4.724	.004	.010
Angina pectoris	-1.485	.001	.407	-2.535	.001	.237
Kidney disease[1]	-2.139	.003	.215	-3.250	.002	.051
BP-medication	-5.272	.076	<0.001	-5.123	.036	<0.001
LV EDV (2D) (ml)	.092	.123	<0.001	.154	.276	<0.001
LV EDV (3D) (ml)	.109	.160	<0.001	.142	.211	<0.001
LV EF (2D) (%)	.248	.043	<0.001	.055	.001	.188
LV EF (3D) (%)	.292	.049	<0.001	.121	.004	.015
Mitral annular S' (cm/s)	2.421	.234	<0.001	1.582	.089	<0.001
(cm/s)	1.362	.140	<0.001	1.666	.267	<0.001
Mitral E/e' ratio (cm/s)	-1.327	.147	<0.001	-1.574	.145	<0.001
TAPSE (cm)	6.030	.115	<0.001	4.197	.050	<0.001
LA ESV (2D) (ml)	-.037	.018	.003	.060	.017	<0.001
LA ESV (3D) (ml)	-.046	.018	.010	.112	.035	<0.001
LA ESV Ch4 (ml)	-.021	.005	.146	.152	.103	<0.001
LV ED InDi (mm)	.215	.022	.001	.450	.077	<0.001
RV ED BasDm (cm)	.873	.005	.187	4.337	.104	<0.001
Valvular disease[2]	-7.409	.046	<0.001	-6.240	.008	<0.001
Adherence LTPA[3]	-1.173	.003	.181	-.877	.002	.056
Inactive[4]	-3.418	.010	.017	-4.490	.013	<0.001
LTPA minutes[5]	-.004	.003	.224	.002	.001	.217

Values are per unit change of the independent variables. Abbreviations: BMI = body mass index; BP = blood pressure; HR = heart rate; HDL-cholesterol = high-density lipoprotein cholesterol; CRP = c-reactive protein; HbA1c = glycosylated haemoglobin; LV EDV = left ventricular end-diastolic volume; EF = ejection fraction; Mitral annular S’ = mean of peak systolic mitral annular septal- and lateral wall; Mitral annular e’ = mean of peak early diastolic mitral annular septal- and lateral wall; Mitral E/e’ ratio = mitral inflow peak early diastolic velocity to Mitral annular e’ ratio; TAPSE = tricuspid annular plane systolic excursion; LA ESV = left atrium end-systolic volume; Ch4 = 4-chamber view; LV ED InDi = left ventricular end-diastolic internal dimension; RV ED BasDm = right ventricular end-diastolic basal diameter; LTPA = leisure time physical activity. [1]Urinary tract infections excluded, [2]Valvular disease: ≥ moderate valvular disease, [3]Adherence to weekly LTPA recommendations, [4]Exercise never or less than once a week, [5]LTPA minutes weighted after exercise intensity.

Table 7 shows the associations of one unit change in different independent variables with change in relative peak oxygen uptake (VO_{2peak}, mL/kg/min) when adjusting for age and sex. The associations are shown for both groups. Age and sex alone, explained 46.5% of the variance in $VO_{2\ peak}$ among AF participants. The respective number for non-AF participants was 49.9%. For each of the individual variables, the confidence intervals of the beta coefficients are overlapping between AF- and non-AF participants. Confidence intervals not being significantly different indicates that the same predictors explain fitness for both groups.

As expected, inactivity had a significant negative impact on fitness for both groups. On the contrary, we did not find a significant association between leisure time physical activity minutes (table 7) or adherence to weekly physical activity recommendations (table 6) and fitness.

The seven variables sex, age, percent body fat, resting heart rate, left ventricular end-diastolic volume and ejection fraction, and inactivity came out as the strongest predictors of fitness, and therefor included in the final equation in table 8. When adjusting for sex and age, the added R squared ranged between 2.1%-18.4% in the AF group, and between 1.9%-20.1% in the non-AF group for the five remaining variables. Out of the five, inactivity came out as the weakest, and percent body fat as the strongest predictor of fitness for both groups.

Table 7. Multivariate linear regression analyses with VO2-peak as the dependent variable

	AF			Non-AF		
Independent variables	**β-coefficient (SD)**	**R^2**	**p-value**	**β-coefficient (SD)**	**R^2**	**p-value**
Sex (men)	6.512 (5.316, 7.708)	.465	<0.001	7.383 (6.782, 7.985)	.499	<0.001
Age (years)	-.463 (-.509, -.418)		<0.001	-.444 (-.469, -.420)		<0.001
Height (cm)	-.054 (-.154, .046)	.466	.290	-.060 (-.112, -.008)	.500	.024
BMI (kg/m2)	-.875 (-1.000, -.751)	.601	<0.001	-.950 (-1.020, -.880)	.642	<0.001
Percent body fat	-.589 (-.656, -.522)	.649	<0.001	-.591 (-.625, -.556)	.700	<0.001
Level of visceral fat	-.900 (-1.002, -.797)	.649	<0.001	-.957 (-1.001, -.903)	.705	<0.001
WC (cm)	-.314 (-.351, -.277)	.645	<0.001	-.355 (-.376, -.335)	.702	<0.001
Systolic BP (mmHg)	-.018 (-.051, .015)	.469	.287	-.058 (-.076, -.041)	.510	<0.001
Resting HR (beats/min)	-.156 (-.196, -.116)	.517	<0.001	-.157 (-.182, -.131)	.538	<0.001
HbA1c (mmol/mol)	-.195 (-.299, -.091)	.477	<0.001	-.290 (-.360, -.221)	.518	<0.001
BP-medication	-1.967 (-3.189, -.745)	.475	.002	-2.509 (-3.424, -1.594)	.507	<0.001
LV EDV (2D) (ml)	-.019 (-.050, .013)	.471	.245	.072 (.045, .099)	.519	<0.001
LV EDV (3D) (ml)	.027 (.006, .049)	.496	.014	.026 (.012, .040)	.528	<0.001
LV EF (3D) (%)	.233 (.144, .322)	.517	<0.001	.161 (.094, .229)	.533	<0.001
Mitral annular S' (cm/s)	1.194 (.857, 1.532)	.512	<0.001	.218 (.024, .413)	.501	.028
Mitral annular e' (cm/s)	.365 (.110, .619)	.475	.005	.787 (.638, .936)	.529	<0.001
Mitral E/e' ratio (cm/s)	-.496 (-.727, -.265)	.504	<0.001	-.486 (-.642, -.329)	.508	<0.001
Inactive[1]	-4.479 (-6.505, -2.453)	.486	<0.001	-5.990 (-7.299, -4.680)	.518	<0.001
LTPA minutes[2]	-.003 (-.009, .002)	.467	.202	.001 (-.001, .004)	.499	.349

Abbreviations: BMI = body mass index; WC = waist circumference; BP = blood pressure; HR = heart rate; HbA1c = glycosylated haemoglobin; LV EDV = left ventricular end-diastolic volume; EF = ejection fraction; Mitral annular S' = mean of peak systolic mitral annular septal- and lateral wall; Mitral annular e' = mean of peak early diastolic mitral annular septal- and lateral wall; Mitral E/e' ratio = mitral inflow peak early diastolic velocity to Mitral annular e' ratio; LTPA = leisure time physical activity.

[1]Exercise never or less than once a week, [2]LTPA minutes weighted after exercise intensity.

In table 8, the seven variables sex, age, percent body fat, resting heart rate, left ventricular end-diastolic volume (LV EDV and ejection fraction (LV EF), and inactivity are included in the same equation. There was a slight change in LV EDV p-value when adding all variables in the same equation, but still highly significant. In addition, there might be an interaction between LV EDV and LV EF, but there could also be an added value by including both.

Together the seven predictors explained 72.3% of the variance in $VO_{2\ peak}$. With a p-value of <0.001, non-AF participants had a greater mean $VO_{2\ peak}$ than AF participants, equivalent to 2ml/kg/min. As seen in table 7, the difference in $VO_{2\ peak}$ between groups cannot be addressed to any of the variables individually. Verified atrial fibrillation had an influence on fitness in this study.

Table 8. Multivariate linear regression analyses with VO2-peak as the dependent variable.

Independent variables	**β-coefficient (SD)**	**p-value**
Sex (1 = men)	2.057 (1.407, 2.707)	<0.001
Age	-.368 (-.389, -.348)	<0.001
Percent body fat	-.525 (-.560, -.490)	<0.001
RHR	-.082 (-.102, -.061)	<0.001
LV EDV	.014 (.004, .024)	.004
LV EF 3D	.098 (.054, .142)	<0.001
Inactive[1]	-3.198 (-4.182, -2.215)	<0.001
[non-AF]	2.032 (1.483, 2.581)	<0.001
[AF]	0	

Abbreviations: RHR = resting heart rate; LV EDV = left ventricular end-diastolic volume; EF = ejection fraction. [1]Exercise never or less than once a week. Variables in brackets = fixed during multivariable analysis.

DISCUSSION

The predictors strongest associated with fitness were the same for AF and non-AF participants. In total, 73.3% of the variation in $VO_{2\,peak}$ were explained by age, sex, percent body fat, resting heart rate, left ventricular end-diastolic volume, left ventricular ejection fraction and inactivity. Adjusted for these factors, the AF participants had a mean $VO_{2\,peak}$ 2mL/kg/min lower than the non-AF participants, indicating that AF had an influence on fitness.

Study population

The sample of participants is larger and consists of a less selected study population than other studies in relation to direct measurements of VO_{2peak}.[21, 22] Yet, we cannot exclude the possibility of selection bias. Participation was voluntary, and the participants were recruited from two different sub-studies, as well as based on a verified or self-reported atrial fibrillation diagnosis. The participants from the fitness sub-study were a selected group of healthy individuals. Hence, they might be a selection of the fittest as a fit person is probably more likely to attend a fitness study than people not performing regular physical exercise. It's also a possibility that the participants in the fitness study were people that had a family history of cardiovascular disease, or that they had "felt something" lately, that made them more prone to attend a study held by a cardiology department. The same could be the case for the participants from the echocardiography sub-study, with a possible selection towards those with a greater possibility of being sick. Often, there is a selection in both directions in studies like this.[23] In general, the AF participants in this study were older and had a higher level of comorbidities associated with reduced fitness. Common AF symptoms, such as palpitations, exercise intolerance, and dyspnoea, may also have prevented patients from engaging in PA. But, regular endurance training accumulated over many years also increases the risk of atrial fibrillation, which might be the case for some of the participants in the AF-group.[24] However, if only the fittest people were included in the non-AF group, we would believe the difference in VO_{2peak} to be greater.

Methods used in this study

The data were collected using standardized protocols and highly detailed information were provided. We have used the best available technology to measure fitness (VO_{2peak} treadmill test),[15] and myocardial function by advanced echocardiography. Three-dimensional volumetric measurements are shown to be robust and such methodology were used in assessment of left ventricular and left atrial volumes as well as left ventricular ejection fraction.

Standardised protocols were used for clinical- and biochemical measurements. Of the body measurements, percent body fat, level of visceral fat, BMI and waist circumference came out strongly associated with fitness, also when adjusting for sex and age. Out of the four, BMI showed the weakest association to fitness (table 7). As the most used measurement of obesity, BMI would have been easier to compare with other studies. But, as percent body fat came out as a stronger predictor, as well as being a more precise and robust measure of obesity, percent body fat was included in the final equation. BMI might show a weaker association because BMI is not an accurate measure of obesity, as it does not discriminate between fat-free mass and fat mass.[25] Rather, it mainly indicates overweight for height. As seen in table 7, height was not a strong predictor of fitness.

Data of leisure time physical activity (LTPA), comorbidities and medications, were collected through self-report questionnaires. The validity of self-reported data varies, and therefore constitutes a possible limitation in this study. Despite this, comorbidities were more present among AF participants, which is in line with previous studies.[2, 3] In contrast, data of LTPA got some contradictory results. As expected, inactivity was negatively associated with fitness. But, the lack of association between fitness and LTPA minutes and adherence to weekly exercise recommendations, were not in line with previous studies,[7, 22, 26, 27] showing that exercise influences cardiorespiratory fitness. It may be several reasons for this lack of associations. It might be because the constructed LTPA-variable made by our group did not match reality, or because of reduced precision of the self-reported data. LTPA minutes and adherence to recommendations are calculated after what intensity the participants reported. It is well known that people tend to paint a bright picture of themselves, exaggerating the true amount of exercise and intensity.[28] In our model, intensity had to be overall graded as low, moderate or high intensity, without the opportunity to nuance each physical activity session. To illustrate, if the participant reported high intensity, all LTPA-minutes were interpreted as high and therefore weighted times two by our model. This gave some of the participants more high-intensity minutes than you expect from a professional endurance athlete. Thus, our model is probably a suboptimal method to quantify LTPA minutes, and not good enough to measure the exact effect of exercise in relations to VO_{2peak}. In relation to adherence to recommendations, it is possible to follow the recommendations, and still have poor fitness, and to have a high degree of fitness and not adhere to the recommendations.[15]

Predictors of fitness

In this study, we found no difference in what predicted fitness regardless of the presence of AF or not. But, after adjusting for the seven most important factors, AF participants still had lower VO_{2peak} than non-AF participants. This is supported by other studies, stating that AF independently predict lower baseline exercise capacity.[27]

In this study, we found a negative association of age, percent body fat, and resting heart rate with cardiorespiratory fitness. Inactivity was also negatively associated with fitness. It is well documented that physical inactivity directly increases the risk of health parameters including poor cardiorespiratory fitness, adiposity and hypertension.[25] Obesity is associated with a significant reduction in CRF [29]. Male sex was associated with a higher level of fitness. This is also in line with previous studies, indicating that men and younger age-groups have a higher absolute and relative VO_{2max}.[30] Other studies supports that CRF decline with age,[31] and the negative association between RHR and CRF.[32, 33] Higher or improved cardiorespiratory fitness is associated with more efficient myocardial function (higher stroke volume) and lower RHR.[34]

Further, we found left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume to be positively associated with fitness. LVEF is calculated as stroke volume (end-diastolic volume minus end-systolic volume) divided by end-diastolic volume, and is a parameter of left ventricular function. The term refers to the percentage of blood that is ejected from a filled ventricle within each heartbeat. Conventional cardiovascular risk factors are associated with LV and RV function, with gradually poorer cardiac function with higher blood pressure, BMI etc.[23] The previous finding that individuals who report high level of exercise across the lifespan have more compliant left ventricles than sedentary, age-matched control subjects supports our findings.[35]

LA enlargement is common in people with AF. This is partly due to higher prevalence of comorbidities that affect LA volume and remodelling, and because AF most commonly is a disease of the elderly. Left atrial (LA) size is part of cardiac remodelling in a variety of cardiovascular diseases and a strong predictor of cardiovascular morbidity and mortality.[36]
Increased LA volume is an independent predictor of exercise intolerance. Many of the comorbidities are associated with reduced fitness.[1] However, in this study LA volume was not a strong predictor of fitness in either group. This may partly be caused by the fact that LA can

be dilated both due to elevated levels of risk factors and by the high flow caused by physical exercise.[37]

Our findings are important given the lack of specific exercise recommendations for AF patients, despite that this group often possesses a high burden of CVD risk factors and comorbidities that would generally benefit from physical activity interventions. Even a modest improvement in VO_{2peak} may be important, as this measure of cardiorespiratory fitness more strongly predict future cardiovascular disease than measures of simple physical activity.[27] Also, chronic exercise makes the myocardium less susceptible to acute ischemia and can prevent and/or reverse cardiac dysfunction occurring with hypertension, myocardial infarction, and advanced age,[26] which are all associated with atrial fibrillation.[3]

Considering this study population, the characteristics are quite similar to those published elsewhere both for AF and non-AF participants.[22, 27] We present similar distribution of BMI, comorbidity and age as many others. Thus, our results could be generalized to other populations.

Strengths and limitations.
The main strengths of the study is the use of validated[11] AF diagnosis from hospital registers and primary care, the equality between sexes and the methodology used to measure cardiorespiratory fitness and cardiac size and function. However, 427 out of 700 AF participants were based on self-reported atrial fibrillation. Further, we do not know what subgroup of atrial fibrillation the participants pose, whether they have paroxysmal, persistent or chronic atrial fibrillation. This challenge the generalisability of our findings within different subgroups of atrial fibrillation.

The most obvious limitation is the cross-sectional study design, which does not allow us to suggest causal pathways, only associations. The self-reported data constitutes another limitation which may have influenced the results for leisure time physical activity and adherence to recommendations for physical exercise.

CONCLUSIONS

In this study, we identified the most important predictors associated with cardiorespiratory fitness, comparing participants with and without atrial fibrillation. The predictors were related to body size, clinical characteristics, echocardiographic measurements and leisure time physical activity measurements. We found no difference in what predicted fitness regardless of the presence of AF or not. After adjusting for the seven most important factors, VO_{2peak} (ml/kg/min) were still 5.7% lower among AF participants than non-AF participants, indicating that atrial fibrillation is associated with lower fitness.

As there was no difference between the predictors of fitness between the groups, the results indicate that AF patients can be advised and treated as non-AF individuals with respect to improve fitness.

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