Lasse Rødal

Peak oxygen uptake and quality of life in patients with atrial fibrillation

Cross-sectional data from the HUNT4 Fitness study

Master's thesis in Physical Activity and Health. Specialization in Exercise Physiology
Supervisor: Bjarne M. Nes
Co-supervisor: Håvard Dalen
May 2021

Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

NTNU
Kunnskap for en bedre verden

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Trondheim, May 2021

Lasse Rødal

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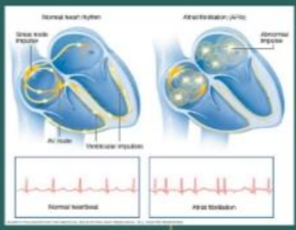
Infographic

Atrial fibrillation

Increases of risk of mortalit, and reduces quality of life



Mayoclinic.org

What is it?

Atrial fibrillation (AF) is the most common arrythmia worldwide, mainly affecting the elderly population. AF is a abnormal contraction of atrium and instead of normal beat, the atrium quiver or fibrillate.

Why?

Research show that patients with AF has increased risk of cardiovascular diseases (CVD) and stroke. Further, patients with AF are more inactive and have reduced quality of life compared to healthy. The aim of this study was to describe exercise capacity in AF patients with and without CVD, and the association between maximum oxygen uptake and health related quality of life (QoL) and symptoms in patients with AF.

How?

- HUNT4 Fitness

large population based cohort-study

2462 participants participating with 2448 participants completed a cardiorespiratory fitness test.

- 2322 participants included in the study

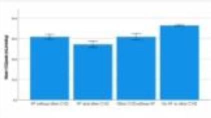
Divided into four groups:

Group 1: AF without other CVD
Group 2: AF with other CVD
Group 3: Other CVD without AF
Group 4: No AF or other CVD

What was the result?

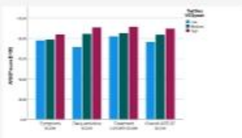
- Reduced oxygen uptake in patients with AF with and without CVD

Table 1.



- Reduced QoL in AF patients with low oxygen uptake

Table 2.



Conclusion

Patients with atrial fibrillation should exercise to increase their maximum oxygen uptake (VO2peak) to increase their quality of life and reduce risk of morbidity and mortality!

What should we do?

Increase level of physical activity

Do more moderate- to vigorous physical activity

Be more social. Spend time with friends and family.

References: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) (Hindricks et al. (2020)); https://www.mayoclinic.org/diseases-conditions/atrial-fibrillation/symptoms-causes/syc-20350624

Sammendrag

Bakgrunn: Kardiovaskulære sykdommer er verdens mest dødelige sykdom som dreper rundt 17.8 millioner personer hvert år. Samtidig så er oksygen opptaket sterkt assosiert med dødelighet og sykdom. Pasienter med atrieflimmer (AF) eller andre hjerte- og karsykdommer (CVD) anbefales å gjøre fysisk aktivitet i henhold til anbefalingene. Disse pasientene har høyere risiko for død og sykelighet, sammenlignet med en sunn befolkning. I tillegg har AF-pasienter lavere maksimalt oksygenforbruk (VO_{2peak}) og lavere livskvalitet (QoL). Derfor var vårt mål å beskrive VO_{2peak} hos pasienter med AF med eller uten annen CVD og sammenligne det med ikke-AF-deltakere. Videre hadde vi som mål å undersøke sammenhengen mellom VO_{2peak} og QoL hos AF-pasienter.

Metode og resultat: Vi brukte data fra en stor populasjonsbasert helse studie (HUNT4 Fitness), og 2322 deltakere (48,1% kvinner) ble inkludert. Deltakerne ble delt inn i fire grupper basert på AF og annen CVD i) AF uten annen CVD (n = 215), ii) AF og annen CVD (n = 89), iii) annen CVD uten AF (n = 92), og iiii) ingen AF eller annen CVD (n = 1926). Gjennomsnittlig VO_{2peak} for de respektive gruppene var i) 32,28 ml / min / kg-1, ii) 28,08 ml / min / kg-1, iii) 31,80 ml / min / kg-1, og iiii) 36,77 ml / min / kg- 1. Generell lineær regresjonsanalyse viste signifikante forskjeller mellom gruppe AF uten annen CVD (-3,00, 95% KI: -3,96, -2,06) og AF og annen CVD (-5,30, 95% KI: -6,73, -3,87) sammenlignet med sunn. AF-pasienter med lav VO_{2peak} har betydelig lavere helserelatert QoL og er flere symptomer plaget sammenlignet med AF-pasienter med høy VO_{2peak}.

Konklusjon: Treningskapasiteten hos pasienter med AF med eller uten annen CVD, ble betydelig redusert sammenlignet med friske i denne store befolkningsbaserte helsestudien. I tillegg er lavt oksygen opptak sterkt assosiert med lav QoL hos AF-pasienter.

Abstract

Background: Cardiorespiratory fitness is strongly associated with mortality and morbidity. Patients with atrial fibrillation (AF) or other cardiovascular diseases (CVD) are recommended to do physical activity. These patients have higher risk of death and morbidity, compared to a healthy population. Additionally, AF patients have lower maximum oxygen consumption (VO_{2peak}) and lower quality of life (QoL). Therefore, our aim was to describe VO_{2peak} in patients with AF with or without other CVD and compare it to non-AF participants. Further, we aimed to examine the association between VO_{2peak} and QoL in AF patients.

Method and results: We used data from a large population-based health-study (HUNT4 Fitness), and 2322 participants (48.1% women) were included. Participants were divided into four groups based on AF and other CVD i) AF without other CVD (n=215), ii) AF and other CVD (n= 89), iii) other CVD without AF (n= 92), and iiii) no AF or other CVD (n= 1926). Mean VO_{2peak} for the respective groups were i) 32.28 mL/min/kg^{-1}, ii) 28.08 mL/min/kg^{-1}, iii) 31.80 mL/min/kg^{-1}, and iiii) 36.77 mL/min/kg^{-1}. General linear regression analysis showed significant differences between group AF without other CVD (-3.00, 95% CI: -3.96, -2.06) and AF and other CVD (-5.30, 95% CI: -6.73, -3.87) compared to healthy. AF patients with low VO_{2peak} have significantly lower health-related QoL and are more symptoms bothered compared to AF patients with high VO_{2peak}.

Conclusion: Exercise capacity in patients with AF with or without other CVD, were significantly reduced compared to healthy in this large population-based health-study. Additionally, low cardiorespiratory fitness is a strongly associated with low QoL in AF patients.

Keywords: Atrial Fibrillation, Quality of Life, Physical Activity

1 Introduction

Conditions that affect heart and blood vessels, defined as cardiovascular disease (CVD), kills an estimate of 17.8 million people each year and represents 31% of all deaths worldwide, making it the deadliest disease globally [1]. Approximately 85% of these deaths are caused by heart attack and stroke [2]. Atrial fibrillation (AF) is the most common arrhythmia of clinical significance and is both a risk factor for adverse CVD and mortality, and a common co-morbidity of CVD. In Europe, AF has approximately 26% chance to occur for men, and 23% chance for women during a lifespan [3].

1.1 Atrial fibrillation

1.1.1 Pathophysiology

During AF episodes, the atrium does not contract in a synchronized rhythm, instead they quiver or fibrillate. The abnormality is caused by ectopic foci firing, which is enhanced by irregular Ca^{2+} handling and changes in autonomic nerve activity and response. However, this often does not cause a permanent AF in an atrium which is in good health, and a structural and/or electrical change is needed to have sustained AF [4]. The change causes the atrium to beat very rapidly and irregularly, leading to a large risk of clot formation. This would cause an embolism in the brain which can lead to a stroke.

Patients with early AF is often triggered by a few ectopic foci. If the ectopic foci firing terminates withing seven days, the patients are diagnosed with paroxysmal AF. When AF lasts more than seven days, it is known as a persistent AF. If the restoration to sinus rhythm is impossible, it is known as permanent AF. Persistent and permanent AF is due to gradual conduction- and anatomical-remodeling in the atria. Continuous and recurrent AF itself will influence electrical conduction and anatomical changes in the atrium. This will increase the number of ectopic foci and re-entry circuits, causing an increase of risk for triggering and maintaining AF. Symptoms of AF include, but are not limited to, palpitations, dyspnea, and fatigue. Patients may also experience chest tightness/pain, dizziness, disordered sleep, or reduced exercise tolerance [5]. Patients with AF could also develop hemodynamically instability, which could cause syncope, acute heart failure, symptomatic hypotension, or cariogenic shock [5].

1.1.2 Incidence and projections

Chugh et al. [6] used the latest Global Burden and Disease, Injuries, and Risk Factors study (GBD 2010) and investigated the incidence of AF in 21 countries worldwide. The study showed that from year 1990 to 2010, the incidence of AF increased from 60.7 per 100 000 person-years to 77.5 per 100 000 person-years in men, and from 43.8 to 59.5 per 100 000 person-years in women. Krijthe et al. [7] makes a prediction and estimates that people with AF will increase to 17.9 million people by year 2060. Approximately 1% of patients with AF are up to 60 years old. The prevalence of AF increases with age, with 3.7% -4.2% of the population between 60-70 years old is affected with AF. However, for people of age 80 years or older, AF is persistent in 10%-17% [3]. Krijthe et al. [7] also anticipated that people above age 75 years with AF increases from 5.6 million in 2010, to 13.8 million in 2060. This may relate to the fact that people live longer, and elderly people having higher prevalence of AF [8]. The prevalence of AF is therefore expected to increase in the coming years, both in Europe and in US [7, 9]. The main reasons to investigate if non-hospitalization treatment can benefit the AF patient group is the fact that this group is hospitalized twice as often as patients without AF, and costs $8700 USD more per year in hospital bills [10].

1.1.3 Risks and comorbidities

AF can occur as a result of an underlying disease, but also without any known diseases. Age and gender are the main risk factors of developing AF, with less risk for women compared to men [5]. Known lifestyle factors as overweight, high blood pressure, diabetes, and inactivity increases the risk for developing AF [5]. However, there are several aspects that could be a potential risk factor of developing AF [5]. Studies show that hypertension, pericardial fat, sleep apnea, thyroid dysfunction, grade of physical activity, and obesity could increase the risk of AF, along with excessive use of alcohol and tobacco [5, 11]. Patients who have developed AF, have 2-23% probability of developing acute coronary syndrome, and may therefore be associated with an increased risk of ST-segment elevation myocardial infarction (STEMI) or non-STEMI acute coronary syndrome [5]. Patients with AF have a five-fold increased risk of stroke or brain hemorrhage [5], whereas the risk of death is doubled [12]. Patients with AF also have an increased risk of heart failure (HF), were HF and AF often coexisting, and trigger each other [5]. In addition, patients with AF may also have a risk of suffering from some form of valvular heart disease [5]. Atherosclerotic vascular disease is commonly seen in patients with AF, while electrolyte disturbances and altered glucose and/or hormone levels in endocrine disorders may increase the chances of developing AF [5]. The increase of morbidity is additionally shown in patients with myocardial infarction or heart failure, when AF is added on the disease pattern [12].

AF patients have commonly lower quality of life (QoL) [13], stemming from reduced social or cerebral function, increased depression or due to increased hospitalizations [5, 12]. Absence of sinus rhythm and acute chest pain or cardiac decompensation could additionally reduce a patient's QoL, reducing the extent of both social- or physical- activity. Furthermore, biopsychosocial factors like dizziness and reduced sleep pattern are associated with QoL in patients with AF. There are few studies on patients with AF and the effect of physical activity (PA). However, the relationship between PA and AF appears to be non-linear [5]. Patients with AF are recommended physical activity at submaximal intensity to decrease AF incidence or recurrence. However, they are not recommended to do excessive endurance exercise [5]. In contrast of that, the effect of exercise-based rehabilitation on death and severe side effects is uncertain [5].

1.2 Exercise and AF

1.2.1 Exercise and VO2peak

Maximum oxygen uptake (VO_{2max}) is commonly known to be a strong predictor of cardiovascular health and mortality [14-16], and has been strongly associated with morbidity and mortality [5, 16]. VO_{2max} decreases with increasing age and at age 60, the mean VO_{2max} for men is 2/3 of that at age 20 years. Further, at around 70 years, the decrease is around 20% per decade [17, 18]. Elderly athletes also experience a decrease in VO_{2max}, and even though this difference is not as severe as non-athletes, the difference is significant [17]. Patients with AF is instructed to induce in PA with moderate intensity to reduce AF related symptoms [5]. However, Garnvik et al. [19] demonstrated significant improvement of all-cause mortality in vigorous PA in AF patients. Further, Malmo et al. [4] established that high intensity interval training reduced the incidence of AF in patients with nonpermanent AF.

1.2.2 PA and risk of atrial fibrillation

It is commonly known that PA reduces the risk of CVD, although, some studies show that with excessive PA, the risk of developing AF is increased [20]. However, the research is limited, and more data is needed to understand the exact cut-off for higher risk and the underlying mechanisms. PA is related to lower risk of CVD [21]. High value for VO_{2max} is a contributor to high cardiac fitness, and there are factors that indicates that excessive and long-term exercise training increases the risk of AF [22]. The majority of the subjects in these studies are male, and the study designs are divergent, resulting in varying estimates in regard to extent of risks, stretching from approximately 20% increase to above 10-fold risk of developing AF [23]. While excessive PA seems to increase the risk of AF, a moderate amount of PA seems to reduce the risk of AF, while inactivity increases the risk [24]. Hence, there seems to be a J-shaped association between the level of PA and AF risk in the general population aged 30-67 years [25]. Furthermore, the study from Morseth et al. [25] showed that there was no significant difference between participants with vigorous PA and inactive individuals. It seems that the level (intensity, frequency and duration) of PA to reduce the risk of AF is low. The same study from Morseth et al. [25] shows that even with second to lowest level of PA (recreational walking or cycling, in less than four hours a week) reduced the risk of AF by 20%. Additionally, a study from Ricci et al [26] showed that participants who exceeded 20 MET (metabolic equivalents of task) hours a week had no reduction on risk of developing AF. A large cohort-study from Jin et al. [27], investigated the effect of PA at different energy expenditures on the incidence of AF. With >500 000 people without AF, 3 443 people developed AF during a median follow-up of 4 years. The study showed that the lowest risk of developing AF was at 500 to 1000 MET minutes a week, corresponding to the general PA recommendations. Subjects who were inactive had the highest risk for developing AF. The study also shows that subjects who performs moderate- to vigorous-intensity leisure-time PA (LTPA), reduces the risk of AF by 12%, compared to inactive subjects. Further, subjects who surpass the minimum recommendations, had no significant AF risk reduction [27]. However, Jin et al. [27] performed a separate intensity model. This showed that intensity have a role where moderate-intensity LTPA significantly reduces the risk for developing AF. There were no significant change after vigorous-intensity LTPA. Jin et al. [27] also demonstrated that with the lowest recommended PA, the risk of mortality, coronary heart disease and HF decreased. With twice as much PA as the minimum recommended level, the risk decreased even more.

1.2.3 Exercise in patients with AF

Patients with AF often report reduced QoL across areas of physical and mental health, as well as limitations in PA [13, 28]. Therapeutic interventions have reportedly increased QoL for patients with AF [29, 30], and recently high intensity interval training appears to reduce time with fibrillation for patients with symptomatic, nonpermanent AF [4].

Typically, people with AF are often more sedentary compared to non-AF people, even though several studies suggest that PA contributes to beneficial health effects for patients with AF [31-34]. A study from Joensen et al. [35] investigated if lack of information on AF for patients with AF, could influence the amount of PA. The study included 58 patients where they completed a rehabilitation program, where qualified personnel informed the patient on pathophysiology, risk factors, treatment, diet, and coping mechanisms for living with AF. They also answered 5 different types of standardized questionnaires, which all had the intention to determine QoL for the subjects. At the end of a 12-month period, the results showed that with more information of the disease, AF patients improved their QoL. The improvement happened during the first 6-months period and during the remaining 6-months of the study, there were no improvement in QoL.

Hegbom et al. [32] conducted a training intervention with three 15-minute training bouts with intensity between 70-90% of HR_{max} for patients with AF. The training bouts included both strength training and stretching at the end of the training session, 3 times a week for 2 months. The results showed that patients with AF who completed the training program, had a significant increase in exercise duration, minutes with exercise, and could continue at higher intensity for a longer duration, compared to inactive patients with AF. The patients also had reduced heart rate at submaximal intensity. This is in line with Joensen's findings [35] where patients with AF improved their 6-min walk test and 5-repetition-sit-to-stand-test. A study from Osbak et al. [34], demonstrated that with a training intensity up to 70% of HR_{max}, patients improved both exercise capacity and resting heart rate, compared to the control group with no activity.

Cardiorespiratory fitness seems to be a precise predictor regarding risk for developing arrhythmia recurrence for overweight people with paroxysmal or persistent AF. Pathak et al. [36] studied 308 overweight people (Body mass index ≥27 kg/m^2) with paroxysmal or persistent AF, over a 49 ± 19-month period. The intention was to evaluate the role of cardiorespiratory fitness and advantage of increasing cardiorespiratory fitness in these obese individuals. They measured the occasion of AF (frequency, duration, and severity) using Severity Scale (AFSS). The study showed that with an increase of ≥ 2MET, and with additional weight loss, the recurrence of AF where 2-fold reduced. With adjustment of weight loss, the reduction of incidence of AF were reduced by 13% compared to the baseline. However, since the duration of this study was long, there might be underlying factors that could affect incidences of AF.

A recent a study looked at the long-term effect of physical activity and estimated cardiorespiratory fitness on all-cause and CVD mortality and morbidity on patients with AF [19]. 1117 patients with confirmed AF were included in the study, with data from the HUNT3 (Nord-Trøndelag Health study). The study showed that patients who had physical activity that met the general PA recommendations [10], had 22% lower risk of CVD morbidity and 30% lower risk of stroke. Furthermore, each 1-MET higher estimated cardiorespiratory fitness, was associated with 12% lower risk of CVD morbidity and 7% lower risk of stroke [19].

1.3 AF and QoL

Several questionnaires specialize in assessing QoL for patients with AF. However, since QoL in patients with AF are complicated and involves several factors, these questionnaires have different structures and limitations [37]. Generally, patients with CVD tends to score low on QoL questionnaires [38]. PA and therapeutic treatment seem to increase QoL in patients with CVD [35]. Garnvik et al [19] showed that compared to the general population, patients with AF had higher risks for all-cause mortality and cardiovascular mortality, if they did not meet the recommended PA. However, if they met the recommendations, they did not have any considerable higher risk for stroke nor all-cause mortality compared to inactive participants without AF. Malmo et al. [4] showed that with high intensity interval training, patients with nonpermanent AF improved their general health and vitality compared to control group, who continued their previous exercise habits. The group who performed high intensity interval training also improved their total measures in physical and mental health, however, this was not significant compared to the control group [4]. Patients with AF are commonly treated with pulmonary vein ablation, cardioversions, and medical treatment [5]. However, these treatments alone have uncertain effect on mortality [4]. In summary PA may work as a supplement, and in some cases, an alternative to medication and invasive procedures, with reduced side effects and complications [4].

1.4 Aims

The aim of the thesis was to describe the exercise capacity, measured as VO_{2peak}, in patients with AF with and without other CVD, and compare it to non-AF participants. Further, we aimed to examine the association between VO_{2peak} and health related QoL and symptoms in AF patients.

2 Method

2.1 Study population and study design

Our study sample stems from a substudy of the Nord-Trøndelag Health study (HUNT), which is a large population based cohort-study for medical and health related research, based in Trøndelag county, Norway. Detailed description of the cohort-study has been explained, and is published elsewhere [39]. In short, the first wave of HUNT started in 1984 and involved citizens based in old Nord-Trøndelag county, Norway. HUNT1 involved participants aged 20 years or older and data collection lasted for 2 years. Moreover, the second wave of HUNT (HUNT2) was carried out between 1995 to 1997, and the third wave (HUNT3) from 2006 to 2008. The number of total participants in all three cohort-studies are 126 159, with over 5000 variables. The fourth wave (HUNT4) started in 2017 and finished in 2019 and included over 56 000 people. HUNT4 Fitness is a substudy of HUNT4, and involved subjects who participated in HUNT3 Fitness (a HUNT3 substudy), and subjects who had AF at contribution in HUNT4. Further, subjects who took part in HUNT4 that (i) also participated in HUNT3 fitness study, (ii) participated in the HUNT3 Echocardiography study or (iii) had either self-reported AF in HUNT4 or diagnosed AF in HUNT3, were included in HUNT4 Fitness. The subjects were invited to a VO2max test and an examination of their heart using ultrasound. 2523 people were invited to contribute in HUNT4 Fitness, where 2448 (97.3%) participated in a VO_{2max} test, out of this 1178 (48.1%) were women. 304 subjects were diagnosed with AF, and divided into 2 groups, AF without other CVD and AF with other CVD. Remaining participants were divided into either group No AF with other CVD which included 92 people, or no AF or other CVD which included 1926 people, respectively.

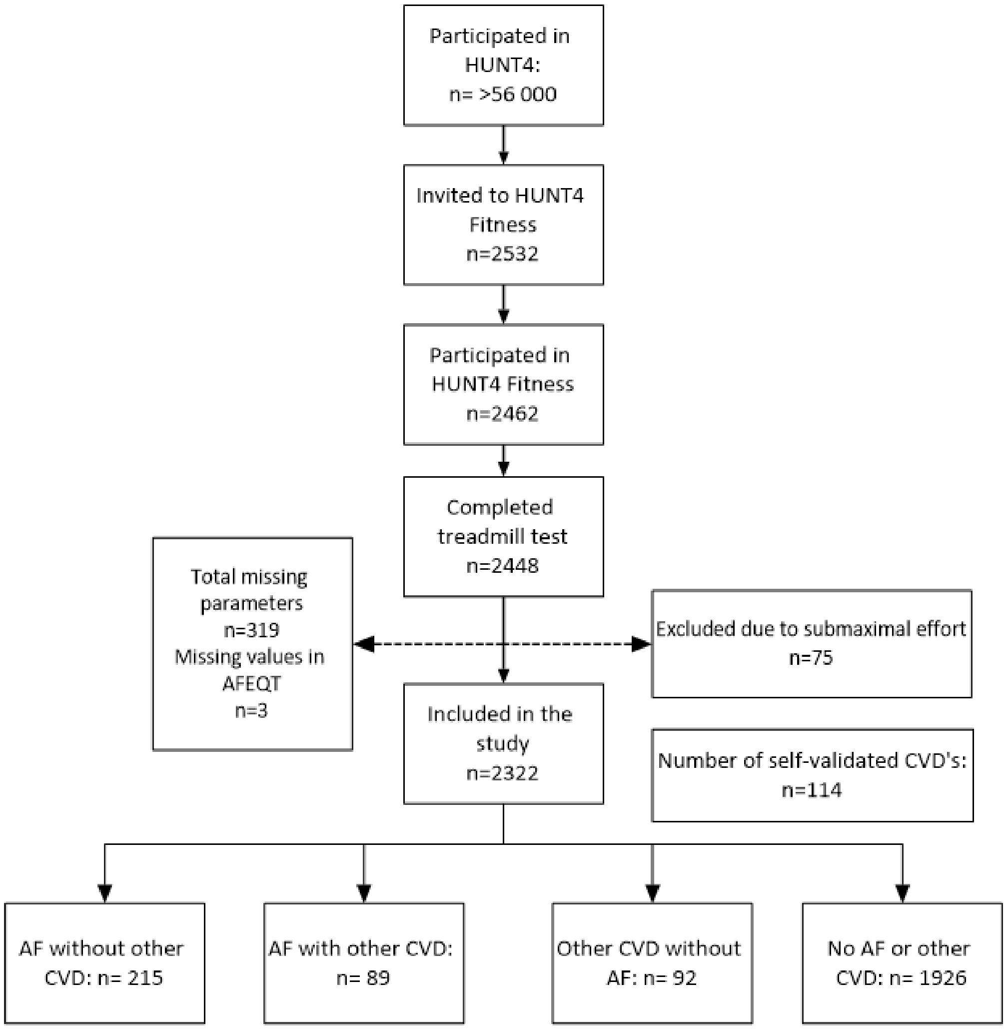


Figure 1. Flow chart of the study population

2.2 Questionnaire-based information

Participants received a questionnaire (Q1) along with the invitation per post. Q1 was answered at home and returned when they attended the basic health examination sites. The data included mapping of disease status and medications, PA, smoking and alcohol habits, among other variables. Cardiovascular diseases and illness included myocardial infarction, heart failure, stroke/brain hemorrhage, diabetes, hypothyroidism, hyperthyroidism, angina pectoris, and kidney disease. The questionnaire was divided into “do you have, or have you had any of the following diseases” and answered by “yes” or “no” at the different CVD’s or illness.

Physical activity was investigated by validated questionnaires in the baseline examination of HUNT4 [39, 40], where exercise is defined by hiking, walking, skiing, swimming, strength training, and sports. The questionnaire includes three domains of PA: frequency, intensity, and duration. Question 1 / 3: How often do you exercise (on average)? (“never” [0], “Less than once a week” [0.5], “once a week” [1], “2-3 times a week” [2.5], and “nearly every day” [5]). Question 2 / 3*: If you exercise as often as once or several times a week: How hard do you exercise? (“Take it easy, I don’t get out of breath or break a sweat [1]”, “I push myself until I’m out of breath and break into a sweat [2]”, “I practically exhaust myself [3]”). Question 3 / 3*: For how long do you exercise each time? (“Less than 15min” [0.10], “15-29 min” [0.38], “3min to 1 hour” [0.75], “more than 1 hour”). PA was calculated based on the values, by multiplying frequency, intensity, and duration. Participants were then classified into recommendations of PA, based on guidelines [41]. The classifications were “above recommendations” (score of 2.5 or above), “belove recommendations” (score of 0 to 2.5), or “inactive” (0). Participants answer who answered “never” or “less than once a week” in frequency, were classified as inactive (0). Calculating smoking were done by stratifying participants into 3 groups; (i) “never smoked”, (ii) “former daily” and “former sometimes”, and (iii) “daily” and “sometimes”. Alcohol was divided into two groups were “2-3 times per week” and “4 times or more per week” was group 1 and “have not consumed alcohol past 12 months”, “one time a month or less”, “2-4 times a month” and “I have never consumed alcohol” was group 2, respectively.

2.2.1 Health related quality of life in AF patients

AF and QoL were calculated using the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire, and has previously been validated [42]. The questionnaire was answered by all participants with valid or self-reported AF at examination site on the day they had cardiorespiratory fitness test. AFEQT is designed to estimate the impact of AF on patient’s health-related quality of life. The participants first answered questions on occurrence to determine the subgroup of AF. QoL questions regarding AF and limitations in the last 4 weeks were reported in Likert-scale, where 1 is “not at all bothered” and 7 “extremely bothered”. AFEQT has 18 questions regarding symptoms, ability to participate in daily activities, and treatment concern. Question 19 and 20 evaluates the satisfaction of treatment and are not included in the overall AFEQT score. Overall score and subgroup score are calculated by the formula below. Calculating subgroup score were done by replacing “sum of severity for all questions answered” in the formula and adding questions regarding either symptoms (question 1-4), ability to participate in daily activities (question 5-12) or treatment concern (question 13-18). Overall score and subscale scores ranges from 0 to 100, where 0 corresponds to totally disability, and 100 to no disability at all. A score change of approximately 5 in either direction is defined as significant change in patient’s health [43].

Formula for calculation of overall- and subgroup- AFEQT score:

$$100 - \left(\frac{(sum\ of\ severity\ for\ all\ questions\ answered - number\ of\ questions\ answered)\ X\ 100}{(total\ number\ questions\ answered\ X\ 6)}\right)$$

2.3 Validation of diagnoses

Participants who had AF at the beginning of HUNT4, was discovered through (i) connection to hospital registers at the local hospitals in Levanger, or Namsos, Norway, or (ii) a valid ECG, including flutter. All participants who checked “yes” for AF in HUNT4 were validated by qualified personnel through connection to hospital registers at the local hospitals in Levanger, or Namsos, Norway. If the patient had AF, but without a valid ECG, or an uncertain diagnosis, patient’s medical records were examined by a qualified medical doctor to confirm of exclude AF diagnosis. Date of occurrence of AF was gathered from their medical journal, and valid diagnosis of AF was defined with ECG. Participants who were diagnosed by their primary care physician but without an ECG, or with a described arrhythmia by their primary care physician, but not validated by medical experts, were classified as "uncertain diagnose" and were excluded from the study. Myocardial infarction was classified by either "acute myocardial infarction without ST elevation", "Myocardial infarction with ST-elevation" or "unknown/other". Further, participants who formerly have had myocardial infarction admission but not with available epicrisis, were diagnosed as "unknown" but with date of admission as "date of incidence". If participants had spasm or spasm-triggered myocardial infarction, but ST-elevation returned to normal within minutes, they were defined as "unknown". Stroke was classified into the following groups: ischemic infarction, parenchymal bleeding, subarachnoid hemorrhage, transient ischemic attack, or uncertain infarction or hemorrhage. With ischemic infarction also including hemorrhagic infarction. The subgroups were later divided into "yes" and "no". Other coronary diseases were classified when there were coronary diseases which did not include unstable angina or coronary artery disease. Heart failure was classified according to ESC 2016 guidelines [44]. Participants with high probability of heart failure, but missing documentation according to ESC guidelines was also included. Use of Betablockers were divided into "daily use" and "discontinuation". With "discontinuation", but without a registered ending date, the ending date was set to middle of the period, which indicates an estimate time of discontinuation.

Based on the known and self-reported diagnoses we formed four separate groups. 1 / 4 "AF without other CVD", consisting of participants with valid AF but no other CVD, 2 / 4. "AF with other CVD", consisting of participants with AF and with other CVD's. Group 3 / 4 consisted of participants with other CVD but without AF ("Other CVD without AF"), and group 4 / 4 formed participants without AF or other CVD's ("No AF or other CVD"). A total of 2322 people were divided into their respective groups (Figure 1). Only those with self-reported AF at examination were further validated for AF and other CVD diagnoses. Hence, the group "Other CVD without AF" consists of participants with predominantly self-reported CVD, although some patients (n=25) had valid CVD, but no AF diagnoses despite self-reporting AF.

2.4 Clinical measurements

Blood pressure (BP) and heart rate (HR) were measured using a Dinamap Carescvape V100. BP and HR were measured three times at a 1-min interval. The average of the second and third measure were used for BP, and the lowest heart rate of the two measurement, were used as heart rate minimum (HRmin). Measurement of weight and height were done at appearance, and body mass index (BMI) were calculated as weight divided by the square of the height in metres (kg/m^2). Blood samples were taken while the participants were non-fasting and analyzed for high-density lipoprotein (HDL) and total cholesterol, glucose (HUNT3 only), glycosylated hemoglobin (HbA1c; HUNT4 only), triglycerides, c-reactive protein, and creatinine.

2.5 VO2peak- measurements

The VO_{2peak} measurements was similar to the protocol used in HUNT3 which is explained elsewhere [39]. Participants did a 10-min warm-up and followed with a stepwise protocol, beginning with two periods of 3 and 1.5min with submaximal intensity. The inclination (1-2%) or speed (0.5-1 km/h) was then increased to voluntary exhaustion. Gas analysis (VO_2, VCO_2, ventilation, breathing frequency, equivalent of O_2, and equivalent of CO_2) was done continuously using the MetaLyzer II (Cortex

Biophysik Gmbh, Leipzig, Germany) mixing chamber system, with the subjects wearing an oro-nasal mask (Hans Rudolph V2, US), which was tested for breathing leakage between each test. VO_{2peak} was defined as the three continuous highest measurements over 30 sec (three 10 sec measurements) and are presented in absolute (L/min) and relative (ml/kg/min) values in Table 3. If the respiratory exchange ratio (RER) was less than 1.0, participants were excluded, indicating a submaximal effort. This is in line with previous studies [45]. HR_{peak} (peak heart rate) was specified as the highest HR observed during the test. After the test, participants answered at what grade they perceived exhaustion using BORG-scale (20-grade scale). After the test, the participant waited for 1 min where Resting heart rate (HRR) were measured.

2.6 Statistical analysis

Statistical analysis was performed using IBM SPSS (Statistical Product and Service Solutions), version 27. Continuous variable with normal distribution is presented as means ± standard deviations (SD), and categorical variables are presented as frequencies (n) and percentages (%). Group comparison were done using general linear model regression analysis (GLM), to assess differences between groups ("AF without CVD", "AF with other CVD", "other CVD without AF" and "no AF or other CVD"). Statistical significance was set to P-value < 0.05. At first a univariate regression was completed to see if there was a significant difference between the four groups in VO_{2peak}, adjusted for sex and age (Model 1). Same analysis was done with BMI, smoking (never, daily and sometimes), alcohol (less or more than 2-3 times a week), minimum heart rate (HR_{min}), and diabetes mellitus as covariates (Model 2). A sensitivity analysis was done including clinical variables that are more likely mediators than confounders in the disease status and VO_{2peak} association (cholesterol, HDL-cholesterol and systolic blood pressure). with negligible changes in the effect estimates.

Additionally, participants were divided into four groups based on age. Group 1 consisted of people up to 39.9 years old. Group 2 consisted of people between 40 years and 59.9 years old. People between 60 years and 74.9 years old formed group 3, whereas group 5 consisted of participants aged 75 years and older.

To examine the association between AF-specific QoL, and VO_{2peak}, we divided the AF participants into sex-specific tertiles of VO_{2peak}. Tertiary VO_{2peak} was divided into high, medium, and low VO_{2peak} based on the results from the cardiopulmonary exercise test. Further, overall score and subscores from the AFEQT questionnaire was calculated using the formula previously explained. The GLM analysis were done with all AFEQT-score subgroups separately (symptoms score, daily activities score, treatment score and overall score) as a dependent variable, and tertiary VO_{2peak} classifications as fixed factors. Two models were constructed with adjustment for age (Model 1) and further adjustment for smoking, alcohol, diabetes, BMI and CVD comorbidity (yes/no). Similar models were constructed stratified by "AF without other CVD" and "AF with other CVD".

3 Results

After excluding for missing VO_2 measurement or submaximal effort (RER < 1.0) after treadmill test, 2322 participants were included in the study (1117 women and 1205 men). Of these, 215 (9.3%) people had AF without other CVD's, 89 (3.8%) people had AF with other CVD's (stroke, infarction, heart failure, or other coronary diseases). 92 (4.0%) of the participants had CVD with no AF, and 1926 (82.9%) had no AF or other CVD, respectively. Baseline data and characteristics stratified by sex and total are showed in Table 1, whereas the characteristics stratified by groups are shown in Table 2.

Results after cardiopulmonary fitness test stratified by sex and groups are presented in Table 3. Other CVD without AF had higher percentages of female (30.4%) compared to AF without other CVD (25.6%) and AF and other CVD (19.1). Mean age was highest in group AF and other CVD (72.4 years) compared to AF without other CVD (66.9 years) and other CVD without AF (67.2 years), respectively. However, AF without other CVD had the highest number of smokers (n = 9), the highest mean BMI (27.5 kg/m^2), and the highest amount of inactive participants in percentages (8.4%) compared to all four groups. Participants in other CVD without AF had the highest percentages of above PA recommendations compared to all groups (other CVD without AF = 70,9%; AF without CVD = 64,4%; AF and other CVD = 62,1 %; No AF or other CVD = 67,4%). Other coronary disease was the highest represented in other CVD (31 (34.8%)), with heart failure as the second highest (29 (32.6%)).

Table 1. Descriptive characteristics of the total population sample

	Women n=1117		Men n=1205		Total n=2322	
Age (years)	59.5	(12.6)	61.4	(12.3)	60.5	(12.5)
Height (cm)	165.7	(5.7)	179.3	(6.3)	172.8	(9.1)
Weight (kg)	70.4	(11.7)	86.0	(12.0)	78.5	(14.2)
BMI (kg/m^2)	25.6	(4.1)	26.7	(3.3)	26.2	(3.8)
Percent body fat	32.8	(7.8)	24.0	(6.5)	28.3	(8.4)
Systolic BP (mmHg)	128.6	(18.8)	133.1	(17.0)	130.9	(18.0)
Diastolic BP (mmHg)	72.7	(9.0)	78.4	(9.9)	75.6	(9.9)
HR_{min} (beats/min)	68.2	(11.1)	65.5	(12.0)	66.8	(11.6)
Cholesterol (mmol/L)	5.6	(1.06)	5.3	(1.08)	5.5	(1.08)
HDL-cholesterol (mmol/L)	1.6	(0.38)	1.3	(0.31)	1.5	(0.38)
CRP (mg/L)	2.0	(4.45)	1.8	(2.71)	1.9	(3.66)
HbA1c (mmol/mol)	33.7	(3.9)	35.1	(5.5)	34.4	(4.88)
Smoking n (%)						
Yes	47	(4.2)	31	(2.6)	78	(3.4)
Former	530	(47.5)	560	(46.5)	1090	(46.9)
No	537	(48.1)	608	(50.5)	1145	(49.3)
Alcohol[a]	284	(25.4)	418	(34.7)	702	(30.2)
PA n (%)[b]						
Above	752	(67.3)	807	(67.0)	1559	(67.1)
Below	289	(25.9)	296	(24.6)	585	(25.2)
Inactive	57	(5.1)	85	(7.1)	142	(6.1)
Beta blockers n (%)	55	(4.9)	97	(8.1)	152	(6.6)
Atrial fibrillation n (%)	72	(6.5)	229	(19.0)	301	(13.0)
Stroke (with AF) n (%)	9 (6)	(0.8)	26 (22)	(2.2)	35 (28)	(1.5)
Infarction (with AF) n (%)	5 (2)	(0.5)	29 (24)	(2.4)	34 (26)	(1.5)
HF (with AF) n (%)	3 (3)	(0.3)	27 (26)	(2.2)	30 (29)	(1.3)
OCD (with AF) n (%)	9 (6)	(0.8)	31 (25)	(2.6)	40 (31)	(1.7)
Self-reported CVD n (%)	15	(1.3)	52	(4.3)	67	(2.9)

[a] More than 2-3 days a week; [b] Above or below recommendations

Values are presented as mean (± SD) or as n (%). BMI = body mass index; BP = blood pressure; HR_{min} = minimum heart rate; HDL-cholesterol = high-density lipoprotein cholesterol; CRP = c-reactive protein; HbA1c = glycosylated haemoglobin; PA = physical activity; HF = heart failure; OCD = other coronary disease; With AF = participants in group AF and other CVD; Self-reported CVD = Participants who checked yes for CVD but are not validated.

Table 2. Descriptive characteristics of the population stratified by AF diagnosis and other known CVD

	AF without other CVD		AF and other CVD		Other CVD without AF		No AF or other CVD	
n (%)	215	(9.3)	89	(3.8)	92	(4.0)	1926	(82.9)
Female n (%)	55	(25.6)	17	(19.1)	24	(26.1)	1021	(53.0)
Age (years)	66.9	(10.0)	72.4	(8.7)	67.2	(8.8)	58.9	(12.4)
Height (cm)	176.5	(8.6)	176.0	(8.7)	175.0	(9.1)	172.1	(9.0)
Weight (kg)	85.8	(14.2)	83.5	(11.4)	82.9	(13.0)	77.4	(14.0)
BMI (kg/m2)	27.5	(3.9)	26.9	(3.2)	27.0	(3.6)	26.0	(3.7)
Percent body fat	27.9	(8.3)	28.7	(7.3)	28.0	(8.7)	28.3	(8.5)
Systolic BP (mmHg)	135.0	(16.8)	136.9	(20.0)	134.5	(18.9)	130.0	(17.9)
Diastolic BP (mmHg)	78.0	(10.0)	77.8	(11.9)	75.4	(9.3)	75.33	(9.8)
HR_{min} (beats/min)	68.0	(14.1)	65.7	(12.5)	64.2	(12.6)	66.9	(11.2)
Cholesterol (mmol/L)	5.2	(1.0)	4.5	(1.12)	4.3	(1.09)	5.6	(1.03)
HDL cholesterol (mmol/L)	1.4	(0.38)	1.3	(0.43)	1.3	(0.36)	1.5	(0.38)
CRP (mg/L)	2.3	(4.39)	2.3	(4.37)	1.4	(2.07)	1.9	(3.59)
HbA1c (mmol/mol)	35.6	(5.73)	37.8	(6.74)	36.2	(5.18)	34.0	(4.55)
Smoking status n (%)								
Yes	9	(4.2)	2	(2.3)	1	(1.1)	66	(3.4)
Former	114	(53.0)	50	(56.2)	48	(52.2)	878	(45.6)
No	92	(42.8)	36	(40.5)	43	(46.7)	974	(50.6)
Alcohol[a]	85	(39.5)	33	(37.1)	31	(33.7)	584	(30.3)
PA n (%)[b]								
Above	143	(66.5)	56	(62.9)	64	(69.6)	1296	(67.3)
Below	53	(24.7)	25	(28.1)	21	(22.8)	486	(25.2)
Inactive	18	(8.4)	4	(4.5)	5	(5.4)	115	(6.0)
Beta blockers (%)	70	(32.6)	45	(50.6)	9	(9.8)	28	(1.5)
Stroke (%)	-		28	(31.5)	7	(7.6)	-	
Myocardial infarction (%)	-		26	(29.2)	8	(8.7)	-	
Heart failure (%)	-		29	(32.6)	1	(1.1)	-	
Other coronary disease (%)	-		31	(34.8)	9	(9.8)	-	
Self-reported CVD n (%)	-				67	(27.2)	-	

[a]More than 2-3 days a week; [b] Above or below recommendations; Values are presented as mean (± SD) or n (%). AF = atrial fibrillation, CVD = cardiovascular disease, BMI = body mass index; BP = blood pressure; HR_{min} = minimum heart rate; HDL-cholesterol = high-density lipoprotein cholesterol; CRP = c-reactive protein; HbA1c = glycosylated haemoglobin; PA = physical activity; Self-reported CVD = participants who checked yes for CVD but are not validated.

Table 3. Cardiorespiratory fitness test stratified in sex and groups.

	Women n=1117 (48.1%)								Men n=1205 (51.9%)							
	AF without other CVD		AF and other CVD		Other CVD without AF		No AF or other CVD		AF without other CVD		AF and other CVD		Other CVD without AF		No AF or other CVD	
n (%)	55	(25.6)	17	(19.1)	24	(26.1)	1021	(53.1)	160	(74.4)	72	(80.9)	68	(63.9)	905	(47.0)
VO_{2peak}(ml/min/kg^{-1})	26.92	(6.86)	24.09	(5.35)	27.20	(5.77)	33.34	(7.60)	34.12	(9.23)	29.02	(7.36)	33.42	(7.74)	40.64	(9.26)
VO_2 (L/min)	1.93	(0.40)	1.82	(0.45)	1.99	(0.45)	2.32	(0.49)	3.02	(0.79)	2.47	(0.65)	2.85	0.69)	3.44	(0.78)
Ventilation (L/min)	70.1	(16.4)	64.7	(15.2)	70.6	(16.2)	79.9	(16.8)	110.0	(23.4)	95.4	(21.5)	108.8	(22.4)	121.7	(24.5
Breathing freq	39.00	(6.42)	38.88	(3.90)	40.58	(5.82)	43.03	(7.36)	41.78	(7.85)	40.14	(7.79)	42.63	(8.64)	44.91	(8.23)
VCO_2 (L/min)	2.06	(0.48)	1.94	(0.50)	2.13	(0.51)	2.53	(0.57)	5.84	(32.90)	2.63	(0.73	3.10	(0.77)	3.79	(1.83)
EqO_2	33.87	(4.73)	32.36	(4.04)	32.85	(4.58)	32.22	(3.93)	34.87	(4.79)	36.81	(5.93)	36.73	(6.19)	33.84	(4.18)
$EqCO_2$	31.80	(4.33)	31.08	(3.53)	30.81	(4.30)	29.60	(3.44)	32.57	(4.72)	34.63	(5.45)	33.82	(5.21)	31.06	(3.72)
HR_{peak}	161.3	(20.6)	149.2	(29.9)	158.9	(16.8)	172.0	(14.6)	167.4	(20.8)	154.5	(23.5)	158.7	(16.6)	172.2	(15.1)
RER_{max}	1.08	(0.05)	1.05	(0.04)	1.09	(0.05)	1.11	(0.05)	1.09	(0.05)	1.08	(0.05)	1.10	(0.06)	1.11	(0.05)
HRR	137.8	(21.7)	121.2	(23.5)	132.3	(17.8)	144.8	(17.2)	140.0	(23.8)	131.2	(24.9)	133.5	(16.0)	143.6	(16.8)
BORG	18.0	(1.5)	18.1	(1.7)	17.8	(1.9)	18.2	(1.3)	18.1	(1.2)	17.6	(1.4)	17.7	(1.4)	18.3	(1.2)

Values are presented as mean (±SD) or n (%). AF = atrial fibrillation, CVD = cardiovascular disease, breathing freq= breathing frequency at VO_{2peak}, VCO_2= Maximum volume of CO_2 at VO_{2peak}, EqO_2= Equivalent of Oxygen at VO_{2peak}, $EqCO_2$= Equivalent of CO_2 at VO_{2peak}, HR_{max}= Maximum registered heart rate, RER_{max}= Maximum registered respiratory exchange ratio, HRR= Heart rate after 1 min recovery after test, BORG= Average result on BORG scale after ended test.

3.1 VO_{2peak} and AF

Mean VO_{2peak} for each group are presented in Figure 2 with 95% confidence interval. Women and men with AF and other CVD had the lowest mean VO_{2peak} (24.09 mL/min/kg^{-1} and 29.02 mL/min/kg^{-1}), respectively. Men in AF without other CVD had the highest VO_{2peak} (34.12 mL/min/kg^{-1}), and women in other CVD without AF had highest (27.02 mL/min/kg^{-1}) compared to healthy (women= 33.32 mL/min/kg^{-1} and men= 40.64 mL/min/kg^{-1}). There were no changes in order when shown in VO_2 (L/min) compared to VO_{2peak} (mL/min/kg^{-1}). AF and other CVD also had the lowest percentages of female in the group (19.1%), respectively.

Participants with AF and other CVD had lowest VO_{2peak} compared to healthy (-5.30, 95% CI: -6.73, -3.87) (Table 4). When we adjusted for confounders, the difference decreased (-4.67, 95% CI: -5.85, -3.48), but still significant (Table 4). Further adjustment for cholesterol, HDL-cholesterol and systolic blood pressure in a sensitivity analysis did not affect the significance.

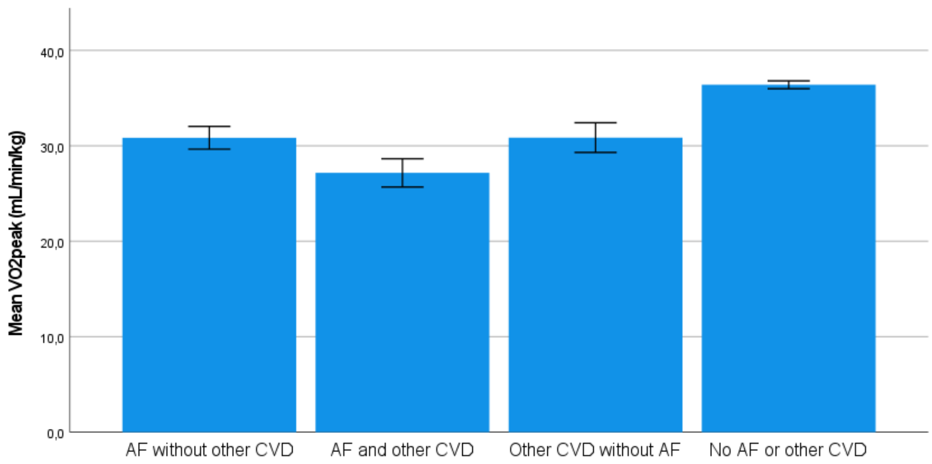


Figure 2. Mean VO_{2peak} for each group with 95% confidence interval.

Table 4. VO_{2peak} across AF and disease status groups

	No AF or other CVD	AF without other CVD	AF and other CVD	Other CVD without AF
Mean (±SD)	36.77 (9.17)	32.28 (9.22)	28.08 (7.26)	31.80 (7.75)
Model 1[a]				
Diff	0 (Ref.)	-3.00	-5.30	-3.34
95% CI	(Ref.)	-3.96, -2.06	-6.73, -3.87	-4.72, -1.95
Model 2[b]				
Diff	0 (Ref.)	-1.80	-4.67	-2.89
95% CI	(Ref.)	-2.58, -1.01	-5.85, -3.48	-4.03, -1.75

[a] Model 1= adjusted for sex and age
[b] Model 2= adjusted for Model 1 + BMI, smoking, alcohol, diabetes and $HR_{min.}$
VO2peak = maximum volume of oxygen registered at cardiopulmonary fitness test, AF = atrial fibrillation, CVD = cardiovascular disease, 95% CI = 95% confidence interval.

Table 5 shows a GLM analysis stratified by sex. Group AF and other CVD had the lowest mean VO_{2peak} regardless of sex (women: 24.09, men: 29.02), respectively. Women in AF without other CVD showed the least difference from healthy (-2.71, 95% CI: -4.33, -1.10), additionally, men in other CVD without AF had the least difference from healthy (-2.85, 95% CI: 4.61, -1.09) (Model 1). Compared to healthy, Women in Other CVD without AF (-3.82, 95% CI: -6.21, -1.44) and men in AF and other CVD (-5.45, 95% CI: 7.19. -3.71) had the highest difference in VO_{2peak}. When we added adjustment for BMI, smoking, alcohol, diabetes and HRmin, the difference reduced in all groups compared to healthy (Model 2). Women in other CVD without AF (-2.58, 95% CI: -4.44, -0.71) and men in AF and other CVD (-4.90, 95% CI: -6.36, -3.44) still had the highest difference in VO_{2peak} compared to healthy. Men in AF without other CVD (-1.45, 95% CI: -2.46, -0.44) had low difference compared to healthy, but still significant. However, difference between women in AF and other CVD and healthy were nonsignificant (-1.58, 95% CI: -3.83, 0.67).

Table 5. Linear regression analysis with VO_{2peak} as dependent variable stratified by sex.

	Women				Men			
	No AF or other CVD	AF without other CVD	AF and other CVD	Other CVD without AF	No AF or other CVD	AF without other CVD	AF and other CVD	Other CVD without AF
Mean (±SD)	33.34 (7.60)	26.92 (6.86)	24.09 (3.35)	27.20 (5.77)	40.64 (9.26)	34.12 (9.22)	29.02 (7.36)	33.42 (7.74)
Model 1[a]								
Diff.	0 (Ref.)	-2.71	-2.91	-3.82	0 (Ref.)	-2.94	-5.45	-2.85
95% CI	0 (Ref.)	-4.33, -1.10	-5.77, -0.06	-6.21. -1.44	0 (Ref.)	-4.15, -1.74	-7.19, -3.71	-4.61, -1.09
Model 2[b]								
Diff.	0 (Ref.)	-1.84	-1.58	-2.58	0 (Ref.)	-1.45	-4.90	-2.67
95% CI	0 (Ref.)	-3.13, -0.55	-3.83, 0.67	-4.44, -0.71	0 (Ref.)	-2.46, -0.44	-6.36, -3.44	-4.13, -1.21

[a] Model 1= adjusted for sex and age
[b] Model 2= adjusted for Model 1 + BMI, smoking, alcohol, diabetes and $HR_{min.}$
VO2peak = maximum volume of oxygen registered at cardiopulmonary fitness test, AF = atrial fibrillation, CVD = cardiovascular disease, 95% CI = 95% confidence interval.

When the groups were divided based on range of age (Figure 3), participants aged 75 years and up had the lowest VO_{2peak} regardless of AF or CVD (AF without other CVD: 23.2 mL/min/kg^{-1}, AF with other CVD: 24.6 mL/min/kg^{-1}, other CVD without AF: 24.3 mL/min/kg^{-1}, healthy: 27.4 mL/min/kg^{-1}). However, participants aged between 60 years and 74.9 years in AF without CVD had the lowest VO_{2peak} (23.2 mL/min/kg^{-1}). The high VO_{2peak} for group < 39.9 in participants with AF without other CVD, is because of one person.

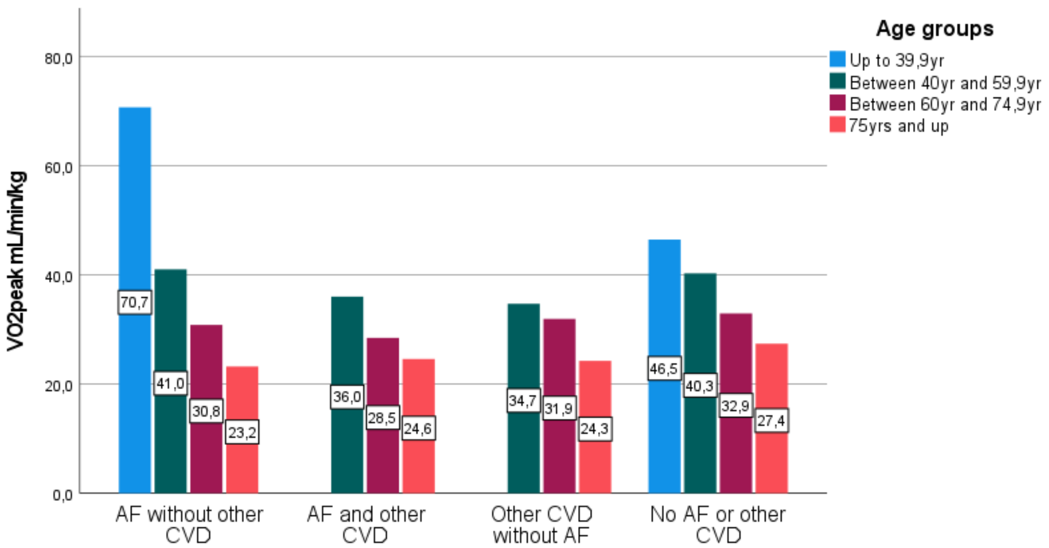


Figure 3. VO_{2peak} presented by age within AF and CVD groups.

3.2 VO_{2peak} and QoL

Mean AFEQT-subscores and overall score divided by high VO_{2peak}, medium VO_{2peak} and low VO_{2peak} are presented in Table 6. Table 7 shows $VO2_{peak}$ tertiles divided in AF without other CVD and AF with other CVD, adjusted for age ([a]) and multiple adjusted (age, CVD/no CVD, smoking, alcohol, diabetes, and BMI) ([b]). The number of answers on each subscore vary. Mean AFEQT-score in all subscores and overall score, for each VO_{2peak} tertiles are shown in Figure 4. AFEQT-scores for AF without other CVD, for each VO_{2peak} tertiles are shown in Figure 5. AFEQT-scores for each VO_{2peak} tertiles in AF with other CVD are presented in Figure 6. When adjusted for age ([a]) and multiple-adjusted (age, CVD/no CVD, smoking, alcohol, diabetes, and BMI) ([b]) there were significant differences between medium VO_{2peak} vs high VO_{2peak}, and low VO_{2peak} vs high VO_{2peak} for all AFEQT-scores. Low VO_{2peak} scored significantly lower on overall score (-16.12, 95% CI: -22.72, -9.52) compared to high VO_{2peak} and medium VO_{2peak} (-8.28, 95% CI: -14.37, -2.20) when adjusted for age. The difference was also present with multi adjustment (low VO_{2peak}: -15.44, 95% CI: -23.13, -7.75, and medium VO_{2peak}: -8.29, 95% CI: -14.86, -1.71). Further, low VO_{2peak} had larger differences in all subscores in both age-adjusted and in multiple-adjusted compared to medium VO_{2peak}. Participants in low VO_{2peak} scored lowest in category daily activities both in mean score (71.17), adjusted for age (-21.38, 95% CI: -29.13, -13.62) and multi adjusted (-19.85, 95% CI: 28.79, -10.92), respectively.

In Table 7, low VO_{2peak} in group AF without other CVD had lowest mean scores on all subscores and overall score (symptoms: 76.26, daily activities: 68.66, treatment concern: 81.31, and overall score: 74,28), compared to all other groups. In group AF without other CVD, symptoms-score, adjusted for age, showed that low and medium VO_{2peak} had significant difference to high VO_{2peak} (low VO_{2peak}: -12.98, 95% CI: -21.99, -3.96, medium VO_{2peak}: -9.04, 95% CI: -17.00, -1.07). However, in group AF and other CVD, low VO_{2peak} there were no significant difference when we adjusted for age (-9.67, 95% CI: -26.16, 6.83), whereas medium VO_{2peak} did show significant difference (-11.97, 95% CI: -28.58, -4.64). When adjusted for multiple confounders ([b]) both medium VO_{2peak} (-11.93, 95% CI: -30.69, 6.83) and low VO_{2peak} (-9.79, 95% CI: -29.53, 9.95) in AF and other CVD showed no significant difference to high VO_{2peak}. In group AF without other CVD, both medium VO_{2peak} (-11.37, 95% CI: -19.93, -2.80) and low VO_{2peak} (-13.89, 95% CI: -24.21, -3.57) showed significant difference to high VO_{2peak}, respectively.

Table 6. AFEQT-scores by sex-specific VO_{2peak} tertiles

	High VO_{2peak} (n=97)	Medium VO_{2peak} (n=100)	Low VO_{2peak} (n=104)
Symptoms score			
Mean	84.47	78.65	78.13
Diff.	0 (Ref.)	-5.86	-6.38
Age-adjusted[a]	0 (Ref.)	-9.56	-11.36
95% CI	(Ref.)	-16.66, -2.46	-19.06, -3.66
Multiple-adjusted[b]	0 (Ref.)	-11.03	-11.57
95% CI	(Ref.)	-18.72, -2.62	-20.52, -2.62
Daily activities score			
Mean	91.00	83.23	71.17
Diff.	0 (Ref.)	-7.80	-19.86
Age-adjusted[a]	0 (Ref.)	-8.96	-21.38
95% CI	(Ref.)	-16.21, -1.70	-29.13, -13.62
Multiple-adjusted[b]	0 (Ref.)	-9.36	-19.85
95% CI	(Ref.)	-17.07, -1.64	-28.79, -10.92
Treatment concern score			
Mean	91.18	85.65	82.35
Diff.	0 (Ref.)	-5.64	-8.95
Age-adjusted[a]	0 (Ref.)	-7.27	-11.05
95% CI	(Ref.)	-12.74, -1.79	-16.89, -5.21
Multiple-adjusted[b]	0 (Ref.)	-6.27	-9.27
95% CI	(Ref.)	-12.06, -0.47	-15.97, -2.64
Overall score			
Mean	89.53	83.44	76.39
Diff.	0 (Ref.)	-6.16	-13.21
Age-adjusted[a]	0 (Ref.)	-8.28	-16.12
95% CI	(Ref.)	-14.37, -2.20	-22.72, -9.52
Multiple-adjusted[b]	0 (Ref.)	-8.29	-15.44
95% CI	(Ref.)	-14.86, -1.71	-23.13, -7.75

[a]Adjusted for age, [b]adjusted for age, CVD/no CVD, smoking, alcohol, diabetes, BMI
AFEQT-score= Atrial Fibrillation Effect on QualiTy-of-life subscore and overall score, AF= atrial fibrillation, CVD= cardiovascular disease, n= number of subjects, 95% CI= 95% confidence interval.

In daily activities score, group AF without other CVD and low VO_{2peak} had high mean difference compared to high VO_{2peak} (-23.05). Further, AF without other CVD showed significant difference in both low and medium VO_{2peak}, when we adjusted for age ([a]) and multiple adjusted ([b]) (low VO_{2peak}: -25.76, 95% CI: -35.00, -16.53[a], -25.30, 95%CI: -35.78, -14.83[b]; medium VO_{2peak}: -12.11, 95% CI: -20.41, -3.81[a], -14.47, 95% CI: -23.21, -5.73[b]) compared to high VO_{2peak}. AF and other CVD showed no significant difference between low VO_{2peak} and medium VO_{2peak} versus high VO_{2peak}, in both age adjusted and multiple adjusted. The same tendency was present in both treatment concern score and overall score, where AF and other CVD showed no significant difference between medium VO_{2peak} and high VO_{2peak}, and low VO_{2peak} and high VO_{2peak}, respectively.

Table 7. AFEQT-score divided into groups with or without CVD and VO_{2peak} tertiles.

	AF without other CVD			AF and other CVD		
	High VO_{2peak} (n=81)	Medium VO_{2peak} (n=75)	Low VO_{2peak} (n=58)	High VO_{2peak} (n=16)	Medium VO_{2peak} (n=25)	Low VO_{2peak} (n=46)
Symptoms (n)	n = 66	n = 55	n = 43	n = 11	n = 17	n = 40
Mean	83.99	79.17	76.26	87.37	76.96	80.14
Diff	0 (Ref.)	-4.82	-7.73	0 (Ref.)	-7.23	-10.41
Age adjusted[a]	0 (Ref.)	-9.04	-12.98	0 (Ref.)	-11.97	-9.67
95% CI	Ref.	-17.00, -1.07	-21.99, -3.96	Ref.	-28.58, -4.64	-26.16, 6.83
Multiple-adjusted[b]	0 (Ref.)	-11.37	-13.89	0 (Ref.)	-11.93	-9.79
95% CI	(Ref.)	-19.93, -2.80	-24.21, -3.57	Ref.	-30,69, 6.83	-29.53, 9.95
Daily activities (n)	n = 64	n = 60	n = 40	n = 13	n = 17	n = 41
Mean	91.70	81.89	68.66	87.50	87.94	74.00
Diff	0 (Ref.)	-9.81	-23.05	0 (Ref.)	0.44	-13.51
Age adjusted[a]	0 (Ref.)	-12.11	-25.76	0 (Ref.)	0.81	-12.81
95% CI	Ref.	-20.41, -3.81	-35.00, -16.53	Ref.	-15.09, 16.70	-28.02, 2.41
Multiple-adjusted[b]	0 (Ref.)	-14.47	-25.30	0 (Ref.)	3.80	-7.82
95% CI	(Ref.)	-23.21, -5.73	-35.78, -14.83	Ref.	-13.39, 20.98	-25.98, 10.35
Treatment concern (n)	n = 67	n = 60	n = 47	n = 12	n = 19	n = 41
Mean	90.14	86.55	81.31	96.99	82.82	83.54
Diff	0 (Ref.)	-3.60	-8.84	0 (Ref.)	-14.17	-13.45
Age adjusted[a]	0 (Ref.)	-4.50	-9.91	0 (Ref.)	-16.31	-16.52
95% CI	Ref.	-10.56, 1.57	-16.66, -3.16	Ref.	-29.12, -3.50	-28.96, -4.08
Multiple-adjusted[b]	0 (Ref.)	-4.96	-9.54	0 (Ref.)	-10.10	-9.64
95% CI	(Ref.)	-11.46, -1.54	-17.27, -1.82	Ref.	-23.74, 3.55	-23.92, 4.64
Overall score (n)	n = 61	n = 53	n = 41	n = 11	n = 15	n = 39
Mean	89.28	83.41	74.28	90.90	83.57	78.60
Diff	0 (Ref.)	-5.88	-15.01	0 (Ref.)	-7.34	-12.30
Age adjusted[a]	0 (Ref.)	-8.48	-18.20	0 (Ref.)	-7.80	-13.09
95% CI	Ref.	-15.21, -1.75	-25.80, -10.61	Ref.	-22.39, 6.80	-27.49, 1.31
Multiple-adjusted[b]	0 (Ref.)	-9.62	-18.50	0 (Ref.)	-3.76	-7.77
95% CI	(Ref.)	-17.12, -2.72	-27.16, -9.78	Ref.	-20.15, 12.62	-25.26, 12,62

[a]Adjusted for age, [b]adjusted for age, smoking, alcohol, diabetes, BMI

AFEQT-score= Atrial Fibrillation Effect on QualiTy-of-life subscore and overall score, AF= atrial fibrillation, CVD= cardiovascular disease, n= number of subjects, 95% CI= 95% confidence interval

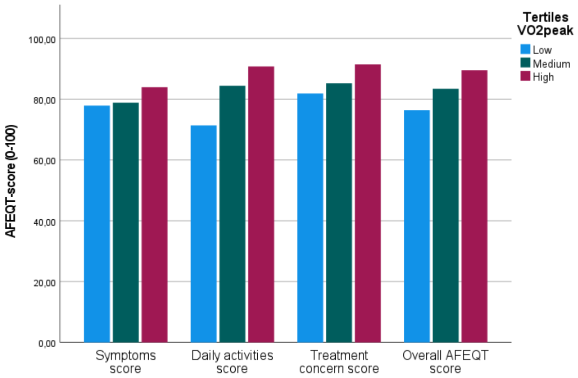


Figure 4. Mean AFEQT-score in subgroups and overall AFEQT-score, with AF without other CVD and AF with other CVD combined, divided in VO_{2peak} tertiles. A score of 100 implies the patient not being bothered at all, and 0 implies extremely bothered.

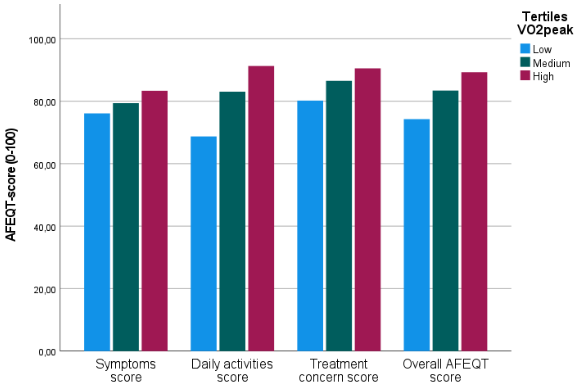


Figure 5. Mean AFEQT-score in subgroups and overall AFEQT-score, in group AF without other CVD, divided into VO_{2peak} tertiles. A score of 100 implies the patient not being bothered at all, and 0 implies extremely bothered.

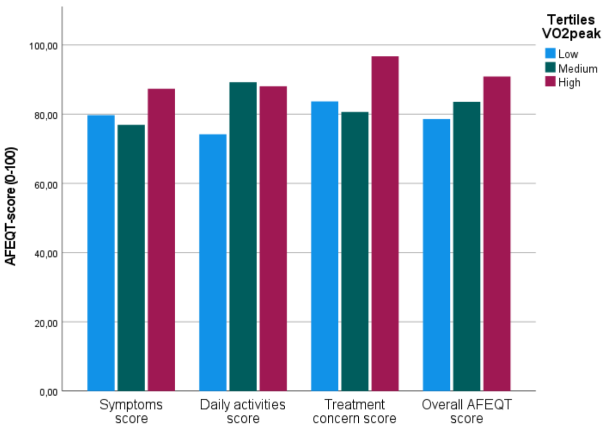


Figure 6. Mean AFEQT-score in subgroups and overall AFEQT-score, in group AF with other CVD, divided into VO_{2peak} tertiles. A score of 100 implies the patient not being bothered at all, and 0 implies extremely bothered.

4 Discussion

4.1 VO2peak and AF

The main purpose of this study was to describe the exercise capacity, measured as VO_{2peak}, in patients with AF with and without other CVD, and compare them to non-AF participants. Further we intended to examine the association between VO_{2peak} and health related QoL and symptoms in AF patients. The study used data from HUNT4 fitness and had 2322 participants, where 301 participants had AF. The main findings of this study demonstrated that participants with AF and other CVD and other CVD without AF had the lowest VO_{2peak} (AF and other CVD: 28.08 mL/min/kg^{-1} ± 7.26, and other CVD without AF: 31.08 mL/min/kg^{-1} ± 7.75). With multi-adjusted model, AF and other CVD had the highest difference to healthy (-4.67, 95% CI: -5.85, -3.48) (Table 4). When stratified by sex men in AF and other CVD had the highest difference compared to healthy (-4.90, 95% CI: -6.36, -3.44), where women in AF and other CVD were nonsignificant (-1.58, 95% CI: -3.83, 0.67) (Table 5). This is inline of previous research where men are more in risk for AF [5], and generally have a higher VO_2 uptake. The major multi-country study Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) looked at real-world practice in recently diagnosed AF patients for risk of stroke/systemic embolism [46]. The study showed that after two years, recently diagnosed AF patients were at high risk of death and stroke. However, stroke only counted for 5.1% of deaths, whereas congestive heart failure, acute coronary syndrome, sudden/unwitnessed death, malignancy, respiratory failure and infection/sepsis accounted for 65% of deaths. This suggests that mortality in AF patients rely more on VO_{2peak} than previously assumed. PA are generally used for prevention and treatment for several CVDs [21]. Hence, with lower number of participants dying of stroke, than from other CVD in the GARFIELD-AF study, VO_{2peak} and PA would reduce risk of mortality in more severe degree. Cardiorespiratory fitness has been shown to be a good indicator to mortality and morbidity in healthy and population with CVD [1, 21], and patients with AF have been recommended to do PA with moderate intensity [5]. Inactivity remains a big risk for AF, and studies show that with meeting the recommendations risk for AF and CVD are significantly reduced [19, 21, 27]. Furthermore, Malmo et al. [4], demonstrated that patients with systematic, non-permanent AF would reduce time with AF and improve VO_{2peak} with high intensity interval training. Even though we do not know the AF subgroups of the patients in this study, one could assume that this is of interest. Additionally, high intensity interval training could reduce AF patients' risk of death and time with AF to an increasing extent compared to recommended guidelines.

AF has higher prevalence in the elderly population [8], this is also representative in this study. With higher mean age in groups with AF without other CVD (66.9 years ± 10.0) and AF with other CVD (72.4 years ± 8.7) compared to healthy (58.9 years ± 12.4). Comparing age difference in the respective groups in Figure 3, shows a clear difference between age, where the elderly has the lowest VO_{2peak} in all groups. This is as expected, since VO_{2peak} reduces with increasing age [17, 18]. CVD increases with age [21] which could explain the higher mean age for group AF with other CVD. Further, a study from Aspvik et al. [47] including 1219 healthy elderly between 70-77 years of age demonstrate that 71% of the participants met the PA recommendations for their age. However, this is based on their own PA recommendation, where age-consideration is included. Without this, only 29% managed to meet the PA recommendations. On both models, elderly with higher levels of cardiorespiratory fitness were more active compared to elderly with lower levels of cardiorespiratory fitness and women were more active than men. Even though the participants in this study are not healthy, one could assume that the amount of PA is lower in group AF without other CVD and AF with other CVD compared to age-matched healthy participants.

Letnes et al. [48] studied the effect of leisure-time physical activity (LTPA) on change of VO_{2peak} and if VO_{2peak} altered the CVD risk factor. The study was based on the same population as this one (HUNT4 Fitness) and looked at the difference between HUNT3 and HUNT4 Fitness Studies. The study concludes that with age VO_{2peak} declines, but that LTPA may slow the decline. Additionally, the study showed that participants that performed high-intensity LTPA, had lower reduction compared to moderate-intensity. The study also showed that high VO_{2peak} was favorable regarding CVD risk factors.

In this study there were no classification of subgroups for AF patients. This could affect the treatment the patients received, where patients with paroxysmal AF is least likely to receive oral anticoagulants [46]. Heart failure (HF) is the most common comorbidity of AF and affects the patient's treatment [46]. Bassand et al. [46] looked at AF patients with HF over 1 year and demonstrated that these patients have greater risk of death by any case. HF often aggravate the prognosis of AF, and vice versa [5], making the treatment more difficult. Treatment for these patients is often medical with Beta-blockers being the most common.

Further, the total group are almost equally divided into female (48.1%) and male. However, when we divided the participants into groups, group AF with other CVD only contained 19.1% of females, whereas patients in AF without other CVD had 25.6% females. With age and gender being the biggest risk for developing AF, where men are more represented, this is as suspected [5].

4.2 VO2peak and QoL

The second investigation of this study was to examine the association between VO_{2peak} and health-related QoL and symptoms in AF patients. On a general basis, patients with AF and low VO_{2peak} had lower QoL and symptoms-score, compared to participants with AF and high VO_{2peak}. AF patients with low VO_{2peak} scored considerably lower on daily activities compared to medium VO_{2peak} and high VO_{2peak}. Previously research have demonstrated that patients with AF rarely induce in regular PA [13, 28], however, it is clearly shown that moderate-intensity PA improves QoL [19]. It is likely to believe that an increase in VO_{2peak} and reduction of incidence of AF would have a positive effect on QoL for the patient. When we adjusted for different confounders, the difference between each subscore remained significant, indicating that an increase in VO_{2peak} would benefit QoL for the patients. Studies shows that patients with AF significantly improves their QoL with exercise [33, 35]. This study contributes to that with higher scores on all subscores and overall score, for group with high VO_{2peak}, taken in concern that group with high VO_{2peak} are more active than low VO_{2peak}.

When we divided the tertile groups, into with or without other CVD, the difference between the subscores in low VO_{2peak} and high VO_{2peak}, and medium VO_{2peak} and high VO_{2peak} were significant (Table 7). However, when we adjusted for age ([a]), and age, smoking, alcohol, diabetes, and BMI ([b]) the difference between subscores in the tertile groups in AF with other CVD became non-significant. This were represented in all subscores and in overall score and when adjusted for all confounders. The results could imply that other CVD in stronger grade interferes with VO_{2peak} than only AF. With AF and HF affecting each other, and HF being the most common morbidity [46], there is likely to believe that this affects both daily activities and symptoms. On a generally basis, PA is recommended for both preventing of CVD and treatment of CVD [21]. Based on this study, PA should also be recommended for increasing VO_{2peak} regarding daily activity, symptom relief, and treatment concern for patients with CVD. However, the low number of patients in different tertiles in AF with other CVD could affect the outcome. Although, we do not know the severity of the CVD nor the amount of mobility, on the patients. Further study should investigate the long term effect of PA on AF patients with and without CVD.

5 Strengths and limitations

The main strength of this study is the population size of validated patients with AF, the number of participants of each group, resemblance of sex and the methodology for cardiorespiratory fitness. However, regarding AF, we do not know what kind of fibrillation the participants have, this could affect the cardiorespiratory fitness test and alter the VO_{2peak} result. It could also be interesting to see the differences between subgroups regarding VO_{2peak}, compared to healthy and other CVDs. Further, the most evident limitation is the cross-sectional study, which limits the opportunity to take casual inference, but only associations. Self-reported data from questionnaires could also affect the outcome of physical activity and the relation PA has on VO_{2peak} in each group. Hence, the number of answers from participants in group AF with other CVD and AF without other CVD, stratified by high, medium, and low VO2peak might vary. Consequently, this could affect the correlation and the level of significance. Some self-reported data yields risk of misclassification. Group other CVD without AF are self-reported and not validated, hence there could several misclassifications even though that group had low VO_{2peak} compared to other healthy. AF and CVD patients that participated in the study may be more healthy and fit than those who chose not to participate. Also, a larger number of AF participants compared to non-AF participants were excluded before testing, aborted testing due to arrythmias or other things, or did not reach RER >1.0, or subjective exhaustion.

6 Conclusion

This study concludes that AF patients have lower VO_{2peak}, both with and without other CVD, compared to healthy. Further, AF patients with other CVD have lower VO_{2peak} compared to participants with only AF. The study also shows that AF patients with low VO_{2peak} have generally lower health-related QoL compared to AF patients with high VO_{2peak}. When divided into with or without CVD, the difference between low, medium and high VO_{2peak} were non-significant in group AF with other CVD, but significant in AF without other CVD in daily activities score, symptoms score and overall score.

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8 Appendix

8.1 AFEQT Questionnaire

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1. **Occurrence of atrial fibrillation** **Name or ID:**______________________

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If **No**, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

__earlier today
__within the past week
__within the past month
__1 month to 1 year ago
__ more than 1 year ago
__I was never aware of having atrial fibrillation

Section 2. The following questions refer to how atrial fibrillation affects your quality of life.

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered Or I did not have symptom	Hardly bothered this	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your: (Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in: (Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

On a scale of 1 to 7, over the past 4 weeks as a result of your atrial fibrillation, how much did the feelings below bother you? (Please circle one number which best describes your situation)

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation treatment, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7

On a scale of 1 to 7, overall, how satisfied are you **at the present time** with:
(Please circle one number which best describes your situation)

	Extremely satisfied	Very satisfied	Somewhat satisfied	Mixed with satisfied and dissatisfied	Somewhat dissatisfied	Very dissatisfied	Extremely dissatisfied
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7
20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Name or ID:____

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