A SEX-BASED EXAMINATION OF THE ACUTE AND CHRONIC EFFECTS OF EXERCISE TRAINING ON PHYSICAL AND MENTAL HEALTH OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION

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A dissertation submitted to the University of Ottawa in partial fulfillment of the requirements for the Doctorate in Philosophy (PhD) degree in Human Kinetics

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ACKNOWLEDGEMENTS

This dissertation would not have been possible without the continuous support from my supervisors, lab colleagues, friends, and family. I am deeply indebted to Drs. Jennifer Reed and Denis Prud'homme for starting this journey with me 4.5 years ago, and for providing me with financial support. After a few emails and videocalls, I landed in Ottawa to embark in one of the most challenging, yet enriching life journeys to date. My most sincere appreciation to my closest supervisor, Dr. Jennifer Reed, who has been by my side amid the up and downs of being an international student and navigating a global pandemic. Jennifer, thank you for taking me on. The best thing about starting my PhD with little research experience is that you have set my standards for how research should be conducted (and they are high quality). Thank you for helping me find a timely field of research that I am deeply passionate about, and for going above and beyond when I needed it the most. I would also like to express my gratitude to the committee members and examiners for taking the time to provide constructive feedback on my projects.

To all my lab colleagues and friends at the University of Ottawa Heart Institute (you know who you are!), I am so lucky to have worked alongside you. I am grateful for your continuous help with my projects, meaningful guidance and encouragement, honest advice, the laughs, and the constructive feedback on my manuscripts and scholarship applications – my achievements have been largely because of you. I am certain these will be life-long friendships. Dr. Andrew Pipe, thank you for your help with our research projects and the tea chats. You are an excellent role model for how to keep your feet on the ground despite reaching the sky. To all our research participants, thank you for your precious time. I have enjoyed getting to know your life stories during our one-on-one exercise sessions.

I am privileged to have received several fundings sources during my studies. Special thanks to the P.E.O. members for their financial and emotional support (*Women helping women reach for the stars).* You have been a wonderful community to connect with. I would also like to thank the University of Ottawa Heart Institute and the School of Human Kinetics at the University of Ottawa for their financial support and opportunities for career growth.

To my academic and non-academic friends who have become my family away from home, thank you for making my time here more joyful and adventurous. Those of you who have taught me about your culture, thank you for helping me become more open-minded and respectful. Multiculturalism is now one of my favourite things about Canada, and it has changed the way I think about our research practices. I also thank my friends from home for offering me the warmest welcome every time I go back – I do not deserve you.

Finally, I am extremely grateful to my family for being the most loving and fun people I know. Thank you for raising me with strong values and for allowing me to build my own path. To my parents, thank you for believing in me and supporting me through my (sometimes) out-of-the-ordinary life decisions. Thank you for all the car rides to my training sessions; my determination and passion for *Physical activity and health* started there. As teachers, sharing your love for education and exercise has taken me where I am today. Mar, Maria, Elena, thank you for being the greatest role models one could ask for, each in your own way. I have faith that we will soon be reunited.

As I continue my research career journey, I strive to continue to make a meaningful, positive impact on those around me.

PREFACE TO THIS DISSERTATION

This dissertation contains data collected as part of three original trials and a systematic review. During my PhD, I was able to contribute to two large randomized controlled trials (Principal Investigator [PI]: Dr. Reed): **(1)** Exercise training in patients with atrial fibrillation - addressing clinical needs (The Opportunity study); and **(2)** Exercise training in patients with persistent and permanent atrial fibrillation (The Exercise-AF study). I was involved in recruitment efforts, and data collection, entry and verification for the Opportunity and Exercise-AF trials (e.g., led and assisted with cardiopulmonary exercise tests, assisted with questionnaire scoring, reduced and processed the physical activity accelerometer data, conducted blood processing in wet labs, led exercise sessions for one of the groups of Exercise-AF). Further, I led the Acute-AF randomized crossover study from inception. I led the research ethics board application, recruitment efforts, coordination of staff and patients, and data collection, entry and verification (e.g., led cardiopulmonary exercise tests, led exercise sessions, scored questionnaires, collected baseline health measures, interpreted ECGs from KardiaMobile devices).

The Covid-19 pandemic starting in March 2020 halted recruitment and data collection on several occasions for the two large randomized controlled trials. Despite the restrictions, Acute-AF recruitment started in January 2022. Given the unprecedented circumstances, I was unable to meet the sample size for two of our four studies. Since the Exercise-AF and Acute-AF trials are ongoing, we anticipate reaching the target sample size for the upcoming manuscript publications.

The following ethics approvals were obtained: **(1)** Opportunity trial: Ottawa Health Science Network Research Ethics Board (protocol #: 20150427); **(2)** Exercise-AF trial: Ottawa Health Science Network Research Ethics Board (protocol #: 20180342); and, **(3)**

Acute-AF trial: Ottawa Health Science Network Research Ethics Board (protocol #: 20210524-01H) and University of Ottawa (protocol #: H-12-22-8737). The work contained in this dissertation is my own, and I take full responsibility for its content.

Funding for the investigator-initiated research trials included: **(1)** Opportunity: Innovations Fund of the Alternate Funding Plan for the Academic Health Sciences Centre of the Ministry of Ontario (PI: Drs. Reed and Nair), New Investigator Award in Clinical Rehabilitation from the Canadian Institutes of Health Research (PI: Dr. Reed), and Heart and Stroke Foundation of Canada Emerging Research Leaders Initiative (PI: Dr. Reed); **(2)** Exercise-AF: Project Grant from the Canadian Institutes of Health Research (PI: Dr. Reed); and, **(3)** Acute-AF: Ottawa Region for Advanced Cardiovascular Research Excellence (PI: Dr. Reed).

During my PhD, I was supported by several funding sources, including the Ministry of Research, Innovation, and Science of the Government of Ontario (PI: Dr Reed) and the Fonds de recherche de l'Institut du Savoir Montfort (PI: Dr Prud'homme). I was also supported by the Philanthropic Educational Organization with an International Peace Scholarship for two academic years, and by the University of Ottawa Heart Institute with a Research Scholarship for two academic years.

DISSERTATION ABSTRACT

Aims and Methods: This dissertation provides insights into the role of sex in the acute and chronic effects of exercise training (ET) in adults with atrial fibrillation (AF). Study 1 used a randomized crossover design to compare short-term changes in AF symptoms between females (F) and males (M) with symptomatic non-permanent AF, when they engaged in one week of high-intensity interval training (HIIT), moderate-intensity continuous training (MICT) or non-exercise Control. Studies 2 and 3 used data from two randomized controlled trials in patients with persistent and permanent AF. Study 2 cross-sectionally compared physical and mental health characteristics between sexes, whilst Study 3 examined sex differences in the effects of 12 weeks of HIIT or MICT on such outcomes. Study 4 was a systematic review comparing changes in physical and mental health outcomes following ET between sexes. **Results:** Study 1 enrolled 17 (35% F) patients. The preliminary findings showed that the overall symptom severity did not significantly differ across study conditions or sex. Study 2 included 78 (50% F) patients. Females had a 27% lower peak aerobic power ($\dot{V}O_{2peak}$), and greater palpitations and resting heart rate. Study 3 included 111 (31% F) patients. Improvements in $\dot{V}O_{2peak}$ (F: +18%, M: +11%) and most outcomes (e.g., quality of life, functional capacity, heart rate, anxiety, depression) did not differ by sex. Study 4 included sex-specific exercise data from 18 studies (868 patients, 29% F). Changes in $\dot{V}O_{2peak}$ following ET did not differ between sexes. AF severity, general health and systolic blood pressure improved significantly less in females after ET. **Conclusions:** (i) exercise does not appear to worsen AF symptoms in the short term; (ii) some sex differences in palpitations and physical health were noted; (iii) improvements in $\dot{V}O_{2peak}$ and several patient-reported and health measures did not differ by sex following ET, yet, our meta-analyses showed that several health outcomes did not improve as much in females as in males following ET; and, (iv) future exercise trials in patients with AF must improve the representation of females.

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LIST OF ABBREVIATIONS

6MWT: Six-minute walk test

ACSM: American college of sports medicine

AF: Atrial fibrillation

AFEQT: Atrial fibrillation effect on quality of life questionnaire

AFSS: University of Toronto atrial fibrillation severity scale

BMI: Body mass index

CCS: Canadian cardiovascular society

CCS-SAF: Canadian cardiovascular society severity of atrial fibrillation scale

CHRS: Canadian heart rhythm society

CI: Confidence interval

CPET: Cardiopulmonary exercise testing

CR: Cardiovascular rehabilitation

CVD: Cardiovascular disease

ET: Exercise training

FFM: Fat-free mass

HADS: Hospital anxiety and depression scale

HIIT: High-intensity interval training

HR: Heart rate

QoL: Quality of life

MCID: Minimal clinically important difference

MCS: Mental component summary

MET: Metabolic equivalent

MICT: Moderate- to vigorous-intensity continuous training, or Moderate-intensity continuous training

MVPA: Moderate- to vigorous-intensity physical activity

PCS: Physical component summary

PPO: peak power output

RCT: Randomized controlled trial

RPE: Ratings of perceived exertion

SAGER: Sex and gender equity in research

SD: Standard deviation

SF-36: Medical outcomes short-form 36

UOHI: University of Ottawa Heart Institute

$\dot{V}O_{2peak}$: Peak aerobic power

CHAPTER 1 - Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1,2] AF is characterized by an irregular heart rhythm and rapid heart rate (HR) arising from electrical conduction disturbances in the atria. Given the rise in AF incidence and prevalence, AF meets the criteria of a 21st-century cardiovascular disease (CVD) epidemic.[3] Such increases result from an ageing population and a rise in the global prevalence of CVD modifiable risk factors, including hypertension, obesity and insufficient physical activity.[4,5] Patients with AF report disabling symptoms and a lower quality of life (QoL) score than those without AF.[6,7] Further, they have a greater risk of stroke,[8] hospitalization[9] and mortality[10] when compared to individuals without AF, leading to a frequent use of healthcare resources.[11] To minimize the burden of AF on patients and the healthcare system, emphasis has been placed on additional, non-invasive treatment strategies for managing patients with AF, such as exercise training.[4,12]

Lifestyle-based therapies are designed to help people change their behaviours and engage in healthy habits to prevent the development or worsening of chronic diseases.[13] Health organizations globally advocate for the use of exercise training for the prevention and management of chronic diseases, including CVD, a leading cause of disability and mortality worldwide.[14–18] Cardiovascular rehabilitation (CR) is a multi-component chronic disease management program with a major focus on exercise training typically lasting between 8 to 24 weeks. CR aims to preserve or resume optimal functioning in society, and slow or reverse the progression of CVD by improving health behaviours (e.g., increasing physical activity levels).[19,20] Lifestyle education and access to health professionals (e.g., exercise physiologists, kinesiologists, physiotherapists, psychologists, social workers, dietitians, smoking cessation counselors) are also offered by many CR programs. Participation in CR is a moderate-to-strong

recommendation following most CVD interventions and diagnoses,[19] but its role in managing patients with AF remains unclear.[21]

Exercise training is a structured, planned, and repetitive subset of physical activity with the aim to maintain or improve physical fitness and/or health.[22] Aerobic exercise training is rhythmic, can be maintained continuously and involves large muscle groups. Engaging in aerobic exercise training has been shown to improve peak aerobic power ($\dot{V}O_{2peak}$), QoL, resting blood pressure, body composition, and symptoms of anxiety and depression in healthy and clinical populations.[23–26] Exercise training can also enhance longevity, with consistent evidence showing a reduced mortality risk in those who regularly engage in physical activity. In support, meeting 150 to 300 minutes per week of moderate- to vigorous-intensity physical activity (MVPA) has been associated with a 19% to 25% lower risk of all-cause, CVD and non-CVD mortality in healthy adults.[27,28] Patients with CVD in the most active tertial have also shown a 30% lower risk of all-cause mortality, when compared to those who were the least physically active.[29] Given the numerous health benefits associated with exercise training, it is often referred to as a "polypill".[25]

Emerging evidence supports some of the aforementioned exercise benefits in patients with AF.[30–38] Improving $\dot{V}O_{2peak}$ with exercise training may be associated with a lower risk of AF recurrence,[39] CVD hospitalization and all-cause mortality in patients with AF.[40] Recent clinical management guidelines have, thus, incorporated exercise training as part of the care of patients with AF.[41–43] Yet, many research gaps remain regarding the role of exercise training as an adjunct therapy to improve the physical and mental health of these patients. The pathophysiology of AF, which often co-exists with several co-morbidities, and the unique HR control challenges may impact the acute and chronic responses to exercise training.[44,45] A major limitation of previous exercise research in patients with AF is the failure to consider the existing

clinical sex differences in AF (e.g., heightened stroke and mortality risk in females than males[46]) when developing exercise trials, where females have been largely underrepresented.[44,47] In turn, the evidence used to develop the management guidelines of patients with AF may not be sex-specific, and current exercise recommendations may not serve females and males with AF equitably.[44,47] Addressing this oversight is a main focus of this dissertation.

1.1. Dissertation aims and structure

The overarching goal of this dissertation was to provide novel insights into potential sex differences (i.e., females when compared to males) in the acute and chronic effects of exercise training on physical and mental health outcomes in adults with AF.

CHAPTER 2: The literature review summarized the exercise literature in adults with AF with a sex-based lens. Research gaps and limitations of previous research trials were highlighted and provided the basis for the following dissertation chapters.

CHAPTER 3: Study 1 compared potential short-term changes in patient-reported AF symptoms during a week of aerobic exercise training when compared to a rest week, between females and males with symptomatic AF. Sex-specific acute responses to exercise in adults with AF were also described. Patients perceive exercise as an AF trigger, they worry that increasing their HR during exercise or overexerting themselves may beget an episode of AF.[48-50] These concerns have been heard throughout the community of patients with AF, yet they have not been thoroughly examined.[41–43] The need for a sex-specific lens was critical as females with AF have been shown to experience more fear and anxiety,[51] and faster HRs at rest and during exercise than males.[52] Further, the acute responses to exercise in patients with AF may be different

because of the unique HR control issues when compared to other CVD populations.[45] The Acute-AF trial was an original randomized crossover study. **The primary purpose of Study 1** was to compare potential short-term changes in patient-reported AF symptoms between females and males with symptomatic AF, when they engaged in a week of aerobic exercise training (i.e., 3 sessions of high-intensity interval training [HIIT] or 3 sessions of moderate-intensity continuous training [MICT]) compared to a week of rest. Since only one case series (N=4 males with permanent AF) to date has described the acute responses to exercise in patients with AF,[45] as secondary aims we sought to describe the sex-specific acute physiological and psychosocial responses (e.g., HR, blood pressure, perceived exertion, anxiety, enjoyment, compliance) to HIIT and MICT in patients with AF. Findings from the Acute-AF study may inform patients and healthcare providers of the typical exercise response in females and males with AF. This is a key first step to understanding and facilitating exercise prescription and participation.

CHAPTER 4: Study 2 compared the physical and mental health profile, and health behaviours between females and males with AF. Several clinical sex differences in patients with AF are well established, such as females having a heightened risk for stroke and mortality than males.[46] Yet, sex differences in many important health measures and behaviours remain unclear in patients with AF (e.g., no studies provide device-measured MVPA levels by sex). Regular MVPA leads to increases in $\dot{V}O_{2peak}$, a predictor of prognosis (i.e., a higher $\dot{V}O_{2peak}$ is associated with a lower mortality risk[40]). A poorer physical and mental health profile, and worse health behaviours such as lower MVPA levels in females with AF than males may contribute to the clinical sex differences in these patients. These associations, however, are understudied. We addressed these research gaps with a cross-sectional observational study. **The main purpose of Study 2** was to compare $\dot{V}O_{2peak}$ (primary outcome), additional physical and mental health characteristics, and

MVPA levels between females and males with AF. To improve our understanding of potential mechanisms of sex differences in the clinical profile, we explored whether $\dot{V}O_{2peak}$ or MVPA levels correlated with the health measures in each sex separately. With the original data provided by Study 2, we hoped to add sex-specific health information to the AF clinical evidence base. Understanding additional sex differences in the physical and mental health profile of patients with AF may inform which health characteristics and behaviours should be preferentially targeted by therapeutic interventions in each sex. Thus, these findings may help to improve precision medicine in patients with AF.

CHAPTER 5: Study 3 compared the effects of 12 weeks of aerobic exercise training on physical and mental health outcomes, and health behaviours between females and males with AF. Several research trials support the chronic physical and mental health benefits of aerobic exercise training in patients with AF.[30–38] Yet, the rare sex disaggregation of research findings[44,47,53,54] and the female under-representation in exercise trials[53,55] may lead to females receiving exercise recommendations without appropriate empirical scientific evidence. The only two exercise trials in patients with AF whose authors reported sex-specific data showed a 10% smaller $\dot{V}O_{2peak}$ improvement in females than males following aerobic exercise training.[56,57] However, no statistical comparisons were conducted between sexes.[56,57] To address this gap in the literature, data from two randomized controlled trials (RCTs) conducted in the Exercise Physiology and Cardiovascular Health Laboratory afforded the opportunity to perform these key sex-based analyses. **The main purpose of Study 3** was to examine potential sex differences in $\dot{V}O_{2peak}$ changes following 12 weeks of aerobic exercise training in the form of HIIT or MICT in patients with AF. Secondary aims compared changes in additional physical and mental health outcomes, and physical activity levels following exercise training between females and males

with AF. With the original data from Study 3, we hoped to provide clinical evidence applicable to both sexes of the efficacy of exercise training to manage the physical and mental health of patients with AF. This work may also provide the foundation for future mechanistic studies that can tease out potential explanations for sex differences in response to exercise training.

CHAPTER 6: Study 4 was a systematic review of the exercise literature in patients with AF using a sex-specific lens. Exercise training contributes to improving the CVD risk factor profile in patients with AF.[44,58] Emerging research in healthy and CVD populations suggests significantly smaller $\dot{V}O_{2peak}$ improvements in females than males following the same exercise training program.[59–65] Yet, some studies show inconsistent findings,[64,66,67] and this has not been systematically reviewed in patients with AF.[44] **The primary purpose of Study 4** was to conduct a systematic review and meta-analysis to compare changes in $\dot{V}O_{2peak}$ following exercise training between females and males with AF. Secondary aims compared changes in patient-reported AF symptoms, QoL, and additional physical and mental health outcomes following exercise training between sexes. With Study 4, we hoped to address the lack of sex-based analyses in previous exercise trials. With several pre-specified sub-analyses, we also hoped to acquire an understanding of the influence of participant or exercise program characteristics on the health effects of exercise training in each sex, with the goal to optimize the exercise prescription for females and males with AF.

CHAPTER 7: The discussion and conclusions. In the final chapter, an integrated discussion, general conclusions and directions for future work were suggested to continue to advance the field of exercise training for the management of patients with AF in a more inclusive and equitable manner.

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CHAPTER 2 - Literature review

2.1. Atrial fibrillation, the most common sustained cardiac arrhythmia

Definition and epidemiology of atrial fibrillation

Atrial fibrillation (AF) is characterized by an irregular heart rhythm and rapid heart rate (HR) arising from an impairment in the electrical conduction pathway within the atria. During an AF episode, several electrical signals are asynchronously fired in the atria, leading to the rapid quivering of these chambers, unorganized atrio-ventricular contractions, and a diminished stroke volume.[1] The AF subtypes are summarized in Table 2.1. Based on the duration of AF episodes, AF is classified as *paroxysmal, persistent, longstanding persistent or permanent*.[2] Over time, paroxysmal AF typically progresses to permanent AF in more than 50% of patients due to the cardiac remodelling secondary to AF episodes (see AF pathophysiology section).[3]

Table 2.1. Classification of atrial fibrillation subtypes.

Paroxysmal AF	A continuous AF episode lasting between 30 seconds and 7 days
Persistent AF	Continuously sustained AF lasting beyond 7 days but less than 1 year
Longstanding persistent AF	Continuous AF for at least 1 year in patients for whom rhythm-control management is being pursued
Permanent AF	Continuous AF for at least 1 year in patients who are not pursuing sinus rhythm restoration

AF: Atrial fibrillation.

Examples of disabling symptoms reported by patients with AF include a low exercise tolerance, dyspnea, lethargy, palpitations and dizziness.[4] Such symptoms contribute to the poor quality of life (QoL) reported by more than 60% of patients.[5] The AF population also has: (i) a 3- to 5-fold increased risk of stroke, as the loss of the "atrial kick" (i.e., the force

generated during late systole to increase the pressure gradient and facilitate blood flow) increases blood stasis in the atria;[6] (ii) frequent hospital admissions (10-40% annual hospitalization rate) from recurrent AF episodes and other co-morbidities that accompany AF;[7] and, (iii) a 1.5- to 3.7-fold increased risk of mortality when compared to adults without AF.[8,9] Thus, this complex arrhythmia poses a substantial burden on patients and the healthcare system, where AF-related expenses are on the rise.[10] Indeed, annual healthcare costs for patients with AF range from 956 million in Canada,[2] €660 to 3,286 million in Europe[11] and $6 to $26 billion in the United States.[12]

More than 37 million people globally[13,14] and more than 450,000 people in Canada are affected by AF.[13] The well-established independent risk factors for AF include aging, hypertension, obesity, heart failure, coronary artery disease, valvular heart disease, diabetes, excessive alcohol consumption and smoking.[15] Poor cardiorespiratory fitness is a novel risk factor. Every additional metabolic equivalent (MET) achieved during treadmill testing has been associated with a 7% lower risk of incident AF (hazard ratio: 0.93, 95% confidence interval [CI] 0.92 to 0.94, $p<0.001$).[16] The importance of risk factor modification is supported by a 14% reduction in the lifetime risk of AF when cardiovascular disease (CVD) risk factors (e.g., hypertension, obesity, diabetes) are absent.[17] Concerningly, AF prevalence is expected to rise by 60% by 2050.[14] This projection is a consequence of an ageing population,[18] better AF diagnostic tools, improved patient survival from cardiac events and procedures, and an increasing global prevalence in insufficient physical activity,[19] hypertension,[20,21] obesity,[21,22] diabetes,[21,23] obstructive sleep apnea,[24] and persistent anxiety and depression.[25]

Pathophysiology of atrial fibrillation and the impact of risk factors

Normal heart rhythm is paced by the sinoatrial node (see Figure 2.1.). A unified contraction of the atria and the ventricles is achieved when an electrical signal follows a specific path:

from the sinoatrial node it travels to the atrioventricular node – which has a limited impulse-carrying capacity thus slowing down the firing rate, the Bundle of His, the left and right Bundle Branches and the Purkinje fibres. During AF, electrical impulses are no longer under the control of the sinoatrial node, causing conduction abnormalities where atrial cells fire as fast as 400 to 600 times per minute at rest, and the ventricular rate may surpass 150 bpm if not medically treated.[26] How these resting conduction abnormalities are affected acutely (i.e., a bout of exercise) or chronically (i.e., a 12 week exercise program) by exercise is unclear. Three main conceptual models explain how AF may develop: focal ectopic activity, single re-entry circuit or multiple re-entrant circuits that perpetuate themselves.[26] A *substrate* for AF is necessary to perpetuate the arrhythmia.[27] Such substrate involves a structural remodelling process in the atria (e.g., inflammation, fat infiltration, fibrosis), and leads to local conduction disturbances and conduction blockages which increase the risk of re-entrant circuits.[27] The electrophysiological basis of AF are beyond the focus of this dissertation.[26]

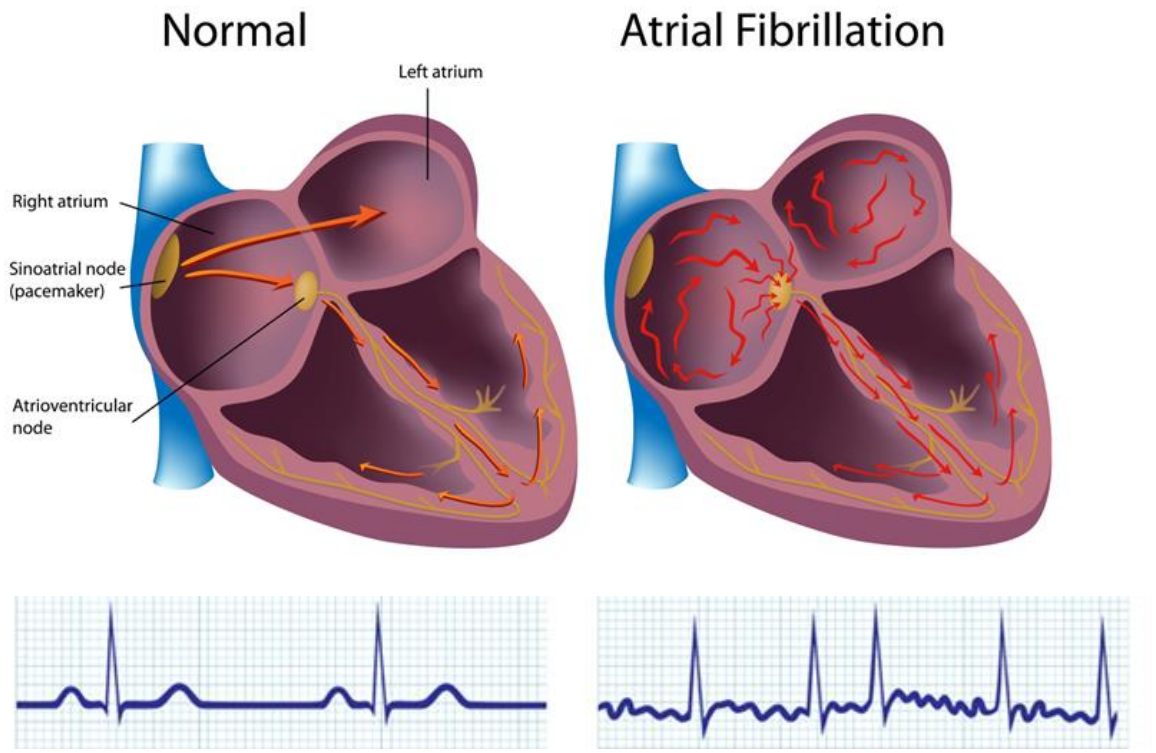

Figure 2.1. Electrical conduction during normal sinus rhythm and atrial fibrillation. Adobe Stock #: 163860726.

Modifiable CVD risk factors play a key role in the pathophysiology and maintenance of AF.[27] Over time, AF leads to electrophysiological, contractile and morphological alterations in the atria (i.e., abnormal substrate).[3,27] Examples of such cardiac remodelling include increased Ca^{2+} entry, decreased duration of the refractory period between action potentials, loss of atrial contractility, atrial dilation, chronic inflammation and increased fibrosis.[1,3,26,28] The presence of modifiable CVD risk factors (e.g., insufficient physical activity,[29] hypertension,[30] obesity,[31] anxiety and depression,[32,33] diabetes,[30] obstructive sleep apnea[24]) accelerates the development[34] and progression of AF[35] by promoting cardiac remodelling.[1,3,26,28,32] Mechanistic research on risk factors associated with AF development is predominantly based on animal models and is not completely understood.[15] For instance, hypertension and obesity have been shown to reduce the atrial conduction velocity, which promotes AF by facilitating re-entry of electrical signals; obesity and sleep apnea increase atrial dilation and pressure; and, obesity and diabetes may lead to disturbances in Na^{+} and Ca^{+} ion currents, prolonging the duration of the action potential and promoting afterdepolarization-related ectopic firing.[15] Further, high body fat is proarrhythmogenic by increasing epicardial fat infiltration in the atria and electrical conduction heterogeneity.[15] Fortunately, the abnormal substrate and atrial remodelling are partly reversible by treating the underlying CVD risk factors.[27] Thus, risk factor modification has been recently incorporated as a major pillar of the care for patients with AF.[2,36,37]

Clinical management of patients with atrial fibrillation

Clinical management of patients with AF aims to reduce the risk of stroke, restore sinus rhythm long-term (rhythm control) and reduce ventricular rate (rate control).[38,39] The overall goal is to improve patients' AF symptoms and QoL.[38,39] Medications (i.e., anti-coagulation, heart rhythm control and rate control) and procedures including cardioversion and catheter

ablation are the principal strategies for managing patients with AF.[2,36,37] Throughout this literature review, I refer to these pharmacological strategies as *traditional treatments*. Electrical cardioversion involves delivering shocks to restore the heart to sinus rhythm. During catheter ablation, scars are created in regions of the atria where abnormal electrical signals are firing, such as the pulmonary veins. In the CABANA trial (N=2,204, 37% females), catheter ablation led to clinically greater improvements in symptom frequency and severity and QoL, when compared to medications for heart rhythm and rate control at 1 year follow-up.[40] Notwithstanding these benefits, the advances in catheter ablation technology and strategies have not translated into significant gains in procedural long-term success rates over recent years. Many patients require repeat procedures[41] and 60% report ongoing symptoms despite these medical treatments.[4,42,43]

The presence of CVD risk factors negatively influences procedural outcomes.[33,44–46] A low peak aerobic power ($\dot{V}O_{2peak}$)[46] and co-morbidities such as metabolic syndrome[44] and heightened depressive symptoms[33] before a cardioversion or ablation have been shown to increase the rates of AF recurrence following the procedures by 25% to 60%. Being aware of these outcomes, addressing such risk factors may benefit patients with AF. In support, multicomponent lifestyle-modification strategies have shown promise in improving patient-reported AF symptoms, QoL and maintenance of sinus rhythm.[37] For instance, patients with overweight or obesity and non-permanent AF (n=150, 32% females) who completed an intensive lifestyle intervention (target: >10% weight loss) had significantly greater improvements in self-reported AF symptom burden, severity and global well-being compared to the control group (i.e., those who received information on risk factor management but no additional support).[47,48] In the intervention group, 33% of patients were free from arrhythmia 2 years following an ablation, when compared to 10% of patients in the control group.[47] In the RACE-3 study (n=246, 21% females), 75% of patients with persistent AF and heart

failure randomized to a risk factor upstream therapy, including CR, remained in sinus rhythm 1 year following a cardioversion, when compared to 63% of those in usual care.[49] In response to these findings, and to address the unmet needs of patients with AF, guidelines have put the assessment and modification of CVD risk factors at the forefront of AF management.[37]

The clinical needs of patients with AF differ across AF subtypes. Symptoms of palpitations, fatigue and dyspnea are most prevalent among those with non-permanent AF.[50] Such symptoms are often mitigated by pharmacological or electrical cardioversion, and/or catheter ablation. However, the long-term success (i.e., sinus rhythm restoration and maintenance) of these traditional treatments decreases as AF progresses from paroxysmal to persistent and to long-standing persistent AF.[50–52] Patients with persistent and permanent AF have been shown to report greater AF burden,[53] and experience more co-morbidities,[50] more advanced cardiac remodelling[54] and a heightened stroke risk than patients with paroxysmal AF.[54] Some evidence suggests a heightened CVD risk profile in patients with persistent and permanent AF when compared to patients with paroxysmal AF (see Figure 2.2.),[50] with a higher prevalence of obesity,[53] physical inactivity[50] and smoking.[50] Further, patients with permanent AF express negative emotions/attitudes knowing that no further treatment options are available.[55] Improving symptom management remains a priority for patients with non-permanent AF, whereas patients with persistent and permanent AF appear to be in the greatest need for improved efficacy of care. Thus, the projects of this dissertation primarily target patients with persistent (4/4 studies) and permanent AF (3/4 studies). Patients with paroxysmal AF are also included in two studies to enhance the generalizability of our work.

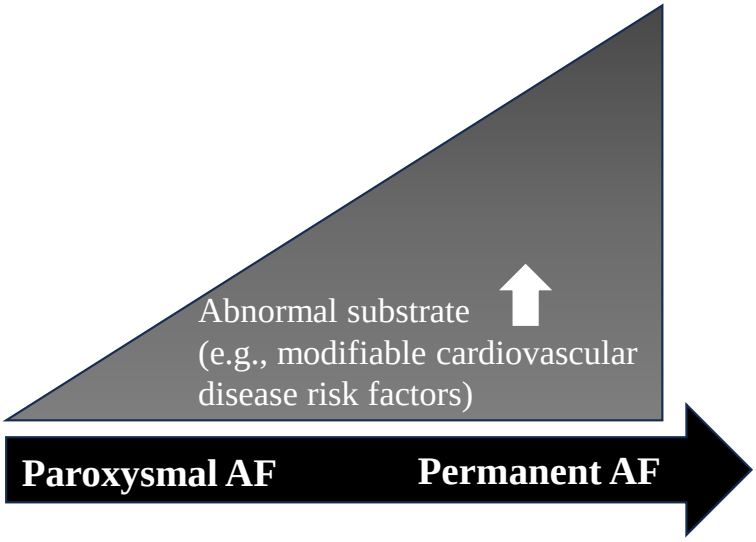

Figure 2.2. A conceptual model of the progression of atrial fibrillation. AF: Atrial fibrillation. As the disease progresses over time, the contribution of abnormal substrates, such as modifiable cardiovascular disease risk factors, prevails.

2.2. Sex differences in patients with atrial fibrillation

Sex- and gender-based terminology

Sex and gender are key determinants of health and disease.[56] The historic male-bias in research (e.g., males serving as the research participant by default) has negatively impacted the health of females for decades, as the foundations of clinical research and care may not be applicable to, and may not have similar benefits for, both sexes.[56–60] The incorporation of sex- and gender-based analyses is increasingly recognized as critical to increase the generalizability and clinical benefits of research findings.[56–60] However, the terminology of sex and gender is evolving and misunderstood by many researchers, hindering the appropriate inclusion of these variables in scientific studies.[61] Sex and gender are two distinct constructs (see Figure 2.3.). Whilst they have been shown to independently influence biological and social determinants of health and disease, sex and gender are often interrelated.[56,61,62] Sex refers to the systematic classification as female, male or intersex assigned at birth based on visual anatomy assessment.[61] Gender refers to socio-cultural traits including roles,

behaviours, activities, identities, and feelings that a given society usually associates with being masculine or feminine. Gender has four dimensions: (1) gender identity; (2) gender roles; (3) gender relations; and (4) institutionalized gender. The examples summarized in Figure 2.3. are not exhaustive; different classifications have been proposed by others.[56,61,62]

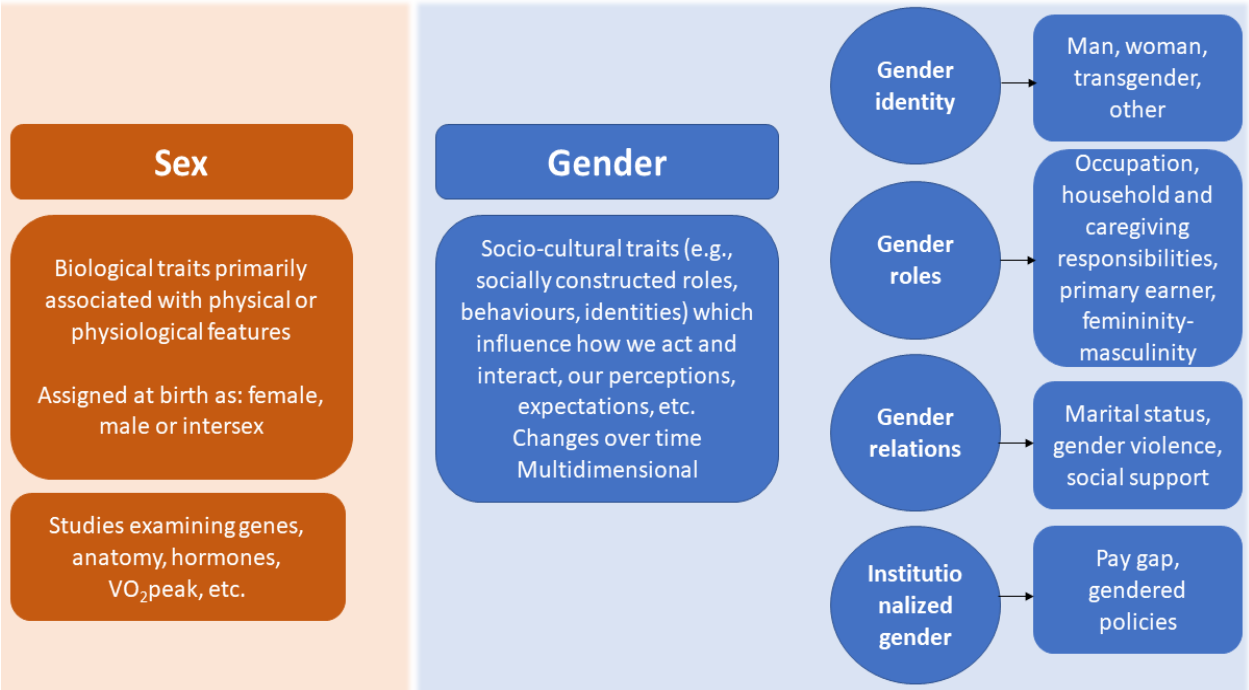

Figure 2.3. Sex and gender terminology. $\dot{V}O_{2peak}$: peak aerobic power.

Both constructs should be measured as, for instance, a feminine gender score but not female sex has been associated with CVD risk factors in cardiac patients.[63] However, most studies do not segregate outcomes by sex or conduct sex-based analyses, fail to consider gender-related factors, and females remain underrepresented across healthy and many disease populations.[58,59,64,65] In AF research, less than 30% of randomized controlled trials (RCTs) reported outcomes by sex between 2011 and 2021, and the participation of females was 12.5% lower than the proportion of females with AF in the general population.[64] In turn, females may be recommended treatment options without appropriate scientific support.[59,64,65]

Sex and gender research guidelines were considered to determine the most appropriate terminology for this dissertation.[56,61,62] The overarching goal of this dissertation is

to offer novel insights into the influence of sex on the role of acute and chronic aerobic exercise training in managing patients with AF. Given the major focus on *sex differences*, the terms *female/male* are used. The term *sex* was chosen as it encompasses a set of biological traits primarily associated with physical or physiological features,[56,61,62] thus, it would reflect several of the measured health outcomes such as $\dot{V}O_{2peak}$. It should be noted that this simplification of describing humans as *female/male* may not align with their gender identity or expression.[61] When available, several *gender-related factors* are incorporated.

Sex differences in patients with atrial fibrillation

Age-standardized AF incidence is greater in males than females.[13,14] Despite the greater risk of AF in males, the absolute number of females and males living with AF is similar, as females generally live longer.[66] Emerging evidence has revealed several clinical sex differences in patients with AF, such that females with AF typically demonstrate worse physical and mental health than males (see Table 2.2.). Females often have a lower $\dot{V}O_{2peak}$,[67] which independently predicts AF recurrence,[68] CVD hospitalization and all-cause mortality.[69–71] Further, females often report more frequent and/or severe AF symptoms,[72–74] a 24% lower QoL after co-morbidity adjustment,[75] and greater symptoms of anxiety and depression.[76] A combination of differences in age (i.e., females develop AF 5 to 10 years later),[74,75,77] sex hormones (e.g., estrogen and progesterone may lead to conduction delay or affect the duration of the action potential)[78,79] and lifestyle behaviours[15,77] (e.g., females tend to be less physically active throughout their lifespan)[80–82] between sexes may explain these disparities. To date, many knowledge gaps exist regarding the pathophysiologic mechanisms accounting for sex differences in patients with AF.[66]

Table 2.2. Sex differences in patients with atrial fibrillation.

♀|♂		Values in females vs. males with atrial fibrillation
Presentation: cardiovascular disease risk factors and co-morbidities	Females are 5-10 years older at the time of atrial fibrillation diagnosis[74,75,77]	
	May have higher prevalence of:	
	Hypertension	74.7% vs. 68.0%*;[74] 85.6% vs. 81.1%*;[75] 63.0% vs. 41.0%*[83], 62.1% vs. 51.1%*;[84] 70 vs. 57%, p=0.002[85]
	Obesity	49.6% vs. 37.3%, p=0.033[77], 40.1% vs. 27.3%*[84]
	Depression	34.8% vs. 23.0%, p=0.017[77]
	Frailty	8.1% vs. 4.1%*[75]
	Poor quality sleep	32.3% vs. 22.0%, p=0.037[77]
	Renal impairment	43.8% vs. 27.2%, p=0.002[77]
	Thyroid disorders	5.2% vs. 3.6%;[72] 11.2% vs. 4.6%, p=0.024[77]
	Valvular heart disease	44.2% vs. 36.1%[72]
	Cognitive impairment	3.9% vs. 2.5%*[75]
	May have lower:	
	% meeting physical activity guidelines	36.7% vs. 55.9% met guidelines*[77] 57% vs. 54% met guidelines, p=0.430[86]
	Peak aerobic power	18.1±6.8 vs. 25.4±7.5 mL O_2/kg/min[67]
	Functional capacity	522±98 vs. 607±100 metres on the 6MWT[67]
	Physical health perception	Physical component summary: 42.7±8.4 vs. 48.0±7.1 points*[67] Physical domain: 18.8±9.2 vs. 21.8±9.5 points*[74]
	Mental health perception	Mental domain: 18.5±8.0 vs. 20.8±7.9 points*[74]
	Quality of life	AFEQT: 80 (62-92) vs. 83 (69-94) points*[75]
	May have higher:	
	Heart rate during atrial fibrillation	126±2 vs. 119±1 bpm, p=0.003,[87] 100±25 vs. 94±22 bpm*[84]
	Anxiety	2.33, 95% CI 1.07 to 3.59**[76]
	Depression	1.48, 95% CI 0.31 to 2.65**[76]
	Additional potential gender-related differences:	
	More females live alone	50.9% vs. 28.7%, p=0.013;[77] 36.0% vs. 15.0%*[67]
	Less females are married	29.6% vs. 59.7%[88]
	Educational level	Lower in females vs. males[77,88]
	Occupation	Lower-skilled occupation in females[77]
Atrial fibrillation-related symptoms	A greater proportion of females are symptomatic	95.4% vs. 89.9;[72] 65.6% vs. 56.8%*;[74] 85% vs. 68%*[73]
	Females may report more frequent or more severe:	
	Palpitations	63.4% vs. 38.5%*;[77] 40.0% vs. 27.0%;[75] 65.2% vs. 44.4%*;[73] 80.0% vs. 69.0%*[89]
	Dizziness	23% vs. 19%*;[75] 26% vs. 14%*;[73] 49% vs. 22%*[67]
	Dyspnea	35.7% vs. 21.8%*[73]
	Lethargy	56.5% vs. 44.3%, p=0.025;[77] 28.0% vs. 25.0%*;[75] 49.1% vs. 32.6%*[73]
	Fear/anxiety	14.6% vs. 10.5%*[74]

Atrial fibrillation therapies	**May be less likely to undergo:**	
	Electrical cardioversion	18.9% vs. 25.5%*[74] 14.9% vs. 20.6%*[72]
	Catheter ablation	6.0% vs. 9.8%, p=0.017[90] 4.9% vs. 5.9%, p=0.04[83] Among patients undergoing ablation, the % of females was significantly lower[84]
	Longer time from diagnosis to referral	6.5±7 vs. 4.9±6.5 years, p=0.02;[91] atrial fibrillation duration: 60 (36-100) vs. 47 (24-74) months, p=0.04[92]
	3x less likely to be referred to a specialized clinic for arrhythmia management[93]	
Health outcomes and prognosis	**May have lower:**	
	Freedom from atrial fibrillation following catheter ablation	F: 20% higher risk of recurrence post-ablation[94] F: lower atrial fibrillation freedom at 2-year follow-up (odds ratio: 0.75, 95% CI 0.69-0.81*)[94] Female sex independent predictor of atrial fibrillation recurrence (hazard ratio: 1.24, 95% CI 1.12-1.38*) at 3-year follow-up[95] CABANA trial: atrial fibrillation freedom did not differ between females (59%) and males (66%) at 12 months[96]
	May have higher:	
	Catheter ablation complication rates	5.0% vs. 2.4%*;[91] 10.2% vs. 7.3%, p=0.013;[97] 9.5% vs. 5.8%*;[94] 2.4% vs. 2.1% p>0.05[96]
	Risk of stroke	4.6-fold higher risk in females[98,99] 20-30% excess risk in females[66,100]
	Risk of heart failure	Increased risk of heart failure in females (relative risk ratio: 1.16, 95% CI 1.07-1.27)[101]
	Risk of hospitalization	Higher risk of hospitalizations after ablation[95]
	Risk of cardiac mortality	2.5-fold higher risk in females[98]
	Risk of all-cause mortality	Inconsistent[75,100] or higher in females: 12% greater risk in females (relative risk ratio: 1.12, 95% CI 1.07-1.17)[101] Male-to-female ratio for mortality: 0.79[102,103]

6MWT: 6-minute walk test; AFEQT: atrial fibrillation effect on quality of life questionnaire; CI: confidence interval. Data presented as proportions, mean ± standard deviation, or median (interquartile range), unless otherwise noted. *: p≤0.001; **: Female sex was associated with higher risk of the measured variable when compared to males.

Females' greater CVD risk factors and co-morbidities may lead to more abnormal AF substrate (e.g., females develop greater fibrosis than males[104]) and reduce the success of clinical procedures.[2] Females have a higher risk of AF recurrence following a catheter ablation,[94] and experience greater side-effects to medications[105] and complications during procedures (see Table 2.2.).[91,97] This may influence the decision-making process, as fewer females undergo cardioversion or ablation procedures than males.[72,74,84] Sex differences in prognosis are noticeable, even after adjusting for age and co-morbidities, females have a higher risk[100] of and more disabling[98,99] strokes, and a higher mortality rate.[98,101,102] Traditional treatments fail to address the inherent sex differences in clinical presentation.[83] For instance, following an ablation females continue to demonstrate lower $\dot{V}O_{2peak}$, worse AF symptoms, self-reported physical health and QoL, and lower 6-minute walk test (6MWT) distance than males.[67,106] Interestingly, the CABANA trial showed a similar proportion of females and males remaining free from AF episodes (67% vs. 66%, p=0.897) 1 year following an ablation.[84] Yet, more females remained symptomatic (50% vs. 40%, p<0.001), continuing to report palpitations, fatigue and dyspnea.[84] Females may particularly benefit from additional therapies that meet their needs. Adjunct strategies may address females' heightened CVD risk factor profile when compared to males, and the sex differences in AF symptoms and QoL that remain after traditional treatments.

Introduction to exercise-based lifestyle therapies to manage patients with atrial fibrillation

Lifestyle-based therapies help patients engage in healthy habits such as regular physical activity, a balanced diet, good quality sleep, limited alcohol intake, and smoking cessation.[107] Guidelines for the management of patients with AF have incorporated lifestyle-based strategies, including exercise recommendations, as a major pillar of patient care.[2,36,37] Regular physical activity is a class IIa (i.e., weight of evidence is in favour of efficacy)

recommendation for the management of CVD risk factors in patients with AF.[36] The 2020 Canadian Cardiovascular Society (CCS)/ Canadian Heart Rhythm Society (CHRS) guidelines recommend that patients with AF engage in at least 200 minutes per week of moderate-intensity aerobic exercise training.[2]

Several multi-component lifestyle interventions with a major focus on exercise training[47,48,68] and exercise-only studies[108–123] in patients with different AF subtypes have been shown to improve $\dot{V}O_{2peak}$, AF symptoms and QoL, and combat CVD risk factors (e.g., elevated blood pressure, body mass, anxiety, depression). Given the notable clinical sex differences in patients with AF, the exercise-focused scientific literature should take sex into consideration to ensure that guidelines for the management of patients with AF, including exercise recommendations, serve females and males with AF equitably.[64,65]

2.3. Exercise, the forgotten therapeutic option for patients with atrial fibrillation

2.3.1. Peak aerobic power, atrial fibrillation, and exercise training

Patients with atrial fibrillation have a diminished $\dot{V}O_{2peak}$, a determinant of mortality

$\dot{V}O_{2peak}$, defined as the highest value of oxygen consumption during an exercise test, is the gold standard measure of cardiorespiratory fitness in clinical populations and refers to an individual's exercise tolerance.[124] $\dot{V}O_{2peak}$ represents how bodily systems work together to meet the increased metabolic demands during exercise. The ability to consume, transport and utilize oxygen is largely influenced by the cardiovascular (e.g., systolic and diastolic function, ventricular-arterial coupling, vascular function), respiratory (e.g., oxygen and carbon dioxide exchange) musculoskeletal (e.g., ability of muscle cells to receive, use and clear oxygen) and nervous (e.g., regulation of blood flow) systems.[125]

$\dot{V}O_{2peak}$ has clinical prognostic implications for those with AF. In patients with non-permanent AF and overweight or obesity, every 1 MET increase in $\dot{V}O_{2peak}$ reduces AF recurrence by 9% after adjustment for changes in body mass and baseline CVD risk factors.[68] A 17% lower risk of CVD hospitalization or all-cause mortality has also been shown with every 1 MET increase following CR.[71] Similar findings have been reported in CVD and heart failure populations: improvements in $\dot{V}O_{2peak}$ of at least 1 mL O_2/kg/min with exercise training are associated with a 7 to 21% reduction in cardiovascular events, re-hospitalization and all-cause mortality.[69,126–128] These associations have led to the consideration of $\dot{V}O_{2peak}$ as a critical vital sign, and a clinically important cardiorespiratory measure to test the efficacy of exercise interventions.[125] $\dot{V}O_{2peak}$, therefore, is a primary outcome of this dissertation.

Patients with AF often have a markedly lower $\dot{V}O_{2peak}$ than other CVD populations (AF vs. non-AF: 14.6±3.1 vs. 19.6±5.1;[114] 16.9±5.2 vs. 20.2±5.5 mL O_2/kg/min[123]). Physiological and behavioural (e.g., physical activity levels) factors may reduce patients' $\dot{V}O_{2peak}$. The atrio-ventricular asynchrony that characterizes AF diminishes cardiac output by 15 to 25% through a reduced stroke volume.[123,129] This is a consequence of the reduction in: (i) atrial contraction and ventricular filling from the shortened R-to-R intervals; and, (ii) end diastolic volume, leading to less stretching of the myocardium and a lower contractile force generated by the heart muscle.[129] Further, the scarce physical activity data suggest that most patients with AF do not engage in sufficient physical activity (i.e., 39% not engaging in any physical activity, 35% occasional physical activity;[130] 40 to 56% reported not meeting the 150 minutes per week recommendation for adults[53,131]), and they accumulate fewer device-measured daily steps than adults without AF.[132]

The evidence supporting the efficacy of exercise training to counteract the diminished $\dot{V}O_{2peak}$ and other CVD risk factors in patients with AF is growing. Trials implementing 90 to 300 weekly minutes of low- to high-intensity exercise training of various modalities (e.g.,

walking, cycling, slow movements), for 6 weeks to 1 year, have led to significant increases in $\dot{V}O_{2peak}$ and functional capacity in patients with various AF types.[133–141]

Increasing physical activity levels is a critical behaviour change to enhance patients' $\dot{V}O_{2peak}$.[131] Regular physical activity has additional benefits: performing more than 30 minutes of moderate- or 20 minutes of vigorous-intensity physical activity at least 1 day per week has been associated with a 10% to 14% lower risk of stroke, and a reduced risk of heart failure and mortality in patients with AF.[142] In the HUNT-3 study (n=1,117 patients, 31% females), patients with AF meeting the physical activity guidelines for adults (i.e., ≥150 minutes/week of moderate, or ≥75 minutes/week of vigorous intensity physical activity)[143] had a 45% lower risk of all-cause and CVD mortality, when compared to those who self-reported being inactive (i.e., physical activity <1 day/week). In the RACE-3 study (n=119 patients with persistent AF and heart failure, 21% females), a CR program led to increases in the proportion of patients meeting the physical activity guidelines from 69% to 88%.[144] Increases in light- and moderate-intensity physical activity have also been observed following 12 weeks of supervised high-intensity interval training (HIIT).[113,145] Yet, other studies have not reported significant physical activity changes following exercise training,[108,121]

Sex differences in $\dot{V}O_{2peak}$ and changes in $\dot{V}O_{2peak}$ following exercise training

In healthy and CVD populations, females often demonstrate a lower $\dot{V}O_{2peak}$,[146–149] even after adjusting for body mass ($\dot{V}O_{2peak}$ 20 to 30% higher in males) and fat-free mass ($\dot{V}O_{2peak}$ up to 15% higher in males).[150] Similar findings have been reported in the sparse data in patients with AF (females: 20.0±5.2; males: 27.7±9.4 mL O_2/kg/min).[67] The sex differences observed in the clinical presentation of patients and their outcomes after traditional treatments may influence the chronic responses of females and males to exercise training. In emerging literature among healthy and CVD populations, several studies have shown that females may

improve $\dot{V}O_{2peak}$ to a lesser extent than males following the same exercise stimulus,[149,151–154] whereas a few trials did not observe differences between sexes.[149,155,156] Sex-specific exercise data in patients with AF are scarce.[67,114] Mertens and Kavanagh (n=20, 35% females) reported a smaller improvement in $\dot{V}O_{2peak}$ in females (7%) than males (18%) in patients with permanent AF following a 12-month walking program.[114] Nearly 20 years elapsed before another exercise trial in patients with AF reported sex-specific outcomes. Wagner *et al*. (n=210, 28% females) found that following exercise-based CR, females experienced a smaller $\dot{V}O_{2peak}$ increase (1.7 vs. 2.9 mL O_2/kg/min) than males, despite females' substantially lower $\dot{V}O_{2peak}$ at baseline. It is noteworthy that none of these studies performed sex-based analyses. In contrast, multivariate analyses of a cohort study (n=292 patients with AF, 24% females) revealed that female sex was a significant predictor of $\dot{V}O_{2peak}$ improvements after CR.[71] The inconsistent and scarce sex-specific exercise data in patients with AF warrants additional studies in this area.

Mechanisms of sex differences in $\dot{V}O_{2peak}$ and changes in $\dot{V}O_{2peak}$ following exercise training – an understudied, conflicting area

$\dot{V}O_2$ is a function of cardiac output (stroke volume x HR; i.e., central factors) – defined as the amount of blood propelled by the left ventricle per minute, and total system arterio-venous oxygen difference (i.e., peripheral factors) – an estimation of the amount of oxygen taken up from the blood by the tissues as shown by the difference in the oxygen content between the arterial and the venous blood. Sex differences seem more pronounced in central than peripheral factors.[157] In older adults, cardiac volume indexes including stroke volume, end diastolic volume and end systolic volume are consistently smaller in females than males during relative work rates.[157] Further, the expected exercise-induced rise in ejection fraction (i.e., % of blood in the left ventricle propelled with each heart contraction) is females is not as

dramatic.[158] The lower reliance on the Frank-Starling mechanism may explain the diminished central adaptations in females after exercise training. Following chronic exercise training, females experience a smaller expansion in blood volume due to impaired baroreflex sensitivity, leading to a lower venous return at a given cardiac preload.[159] Combined with the smaller increase in left ventricular mass and size, females experience smaller improvements in the Frank-starling curves[160] and subsequent changes in stroke volume, cardiac output and $\dot{V}O_{2peak}$.[151] Such mechanisms align with research by Spina *et al*., who showed that exercise-induced changes in left ventricular hypertrophy and β-adrenergic-mediated contractile function were blunted in females.[161]

Several differences in peripheral factors have also been noted. In addition to the smaller heart size and lower muscle mass, females have a 15 to 20% lower blood volume, and lower capillary density per muscle area,[162] muscle fibre size and hemoglobin concentrations (lower arterial oxygen content), which limit the delivery and extraction of oxygen.[146,151,163] Females also have a reduced respiratory function[153] as shown by a smaller diffusion capacity and pulmonary capillary blood volume,[164] and higher work of breathing and oxygen uptake of the respiratory muscles for a given minute ventilation during exercise.[165] Peripheral rather than central improvements following exercise may be more pronounced in females,[166] and this may be age dependent: young females have been shown to rely more on increases in cardiac output, and older females on a widened arterio-venous oxygen difference to improve $\dot{V}O_{2peak}$.[167,168] Sub-group analyses of a meta-analysis in healthy older adults revealed that an increase in the maximum cardiac output was the main determinant of the $\dot{V}O_{2peak}$ increase in males following aerobic exercise training (standardized mean difference: females, 0.31, 95% CI -0.21 to 0.83; males, 0.74, 95% CI 0.44 to 1.04), while in females it was mainly driven by an increase in the arterio-venous oxygen difference (standardized mean difference: females,

0.92, 95% CI 0.34 to 1.50; males, 0.31, 95% CI 0.01 to 1.01).[166] Thus, even when females and males improve $\dot{V}O_{2peak}$, the pathways leading to this increase may differ by sex.

Differences in sex hormones further contribute to the sex-disparity in baseline $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ changes with exercise training.[146,151,163] For instance, testosterone concentrations are significantly higher in males and are augmented following exercise,[169] allowing for greater exercise-induced cardiac and skeletal muscle hypertrophy in males when compared to females.[160] This mechanistic area remains misunderstood as studies investigating the impact of sex hormones on exercise-induced muscle adaptations have predominantly focused on males and pre-menopausal females.[170,171] Following menopause, females experience a greater loss in cardiac, vascular and mitochondrial function than age-matched males.[172] For instance, older females (≥60 years old) experience a greater decline in left ventricular relaxation, causing an impaired diastolic filling, and in vascular conductance.[152,153,173] Estrogen loss has also been shown to limit the exercise-induced vasodilation[151] through an increase in arterial stiffness and a decreased availability of endothelial nitric oxide synthase.[153,173]

Menopause also impacts mitochondrial function. The stimulation of mitochondrial biogenesis in skeletal muscles is an important health benefit from exercise training.[174] Few mechanistically-driven studies have examined sex differences in mitochondria function during or after exercise, and most have used animals. Some research proposes a pre-menopausal female advantage, with sex differences in oxidative capacity (females: higher intracellular lipid content and utilize more fatty acids during exercise[148]), Ca^{2+} handling (females: lower Ca^{2+} uptake) and resistance to oxidative stress (females: more efficient mitochondria, produce less reactive oxygen species and more antioxidants through estrogen receptors).[174] Yet, this female advantage disappears with the postmenopausal estrogen loss, when the oxidative metabolism is impaired through a decline in the expression of key mediators of mitochondrial biogenesis such as peroxisome proliferator-activated receptor-

gamma coactivator 1 alpha (PGC-1α), adenosine monophosphate-activated protein kinase (AMPK), and an increase in reactive oxygen species.[152,160,174,175] These examples underscore the need to report and consider the age and menopausal status of the participants when discussing sex differences in exercise physiology.

Such mechanisms may play a role in sex differences in baseline $\dot{V}O_{2peak}$ and $\dot{V}O_{2peak}$ changes with exercise training in healthy and CVD populations. However, they have not been explored in the AF population, and the relative contribution of each factor is unclear. Sex seems an important, yet not understood factor in the fields of AF and exercise physiology.

2.3.2. Patient symptoms and quality of life, atrial fibrillation and exercise training

Importance of patient-reported outcomes

AF symptoms and QoL are critical patient-reported outcomes (PROs), and a major focus of the clinical management of patients. AF symptoms cause worry and frustration, and prompt patients to seek medical care.[176] Following traditional therapies, 60% of patients with AF report ongoing symptoms,[42,50] and poorer QoL when compared to healthy[177] and other CVD populations.[120] Despite calls to integrate PROs in clinical trials and care to create a holistic approach that facilitates shared decision-making, *hard* clinical endpoints (e.g., AF burden, mortality) continue to be prioritized to evaluate the efficacy of health interventions.[178–180] In support, only 1 in 7 studies in Clinicaltrials.gov in the last 20 years included PROs.[178] This is a gap in the care of patients with AF, as there are medical, economic and ethical reasons for prioritizing research that aims to increase QoL rather than quantity of life.[181]

Effects of exercise training on symptoms and quality of life in patients with AF

Several studies to date highlight the potential of exercise training to improve AF symptoms[109,113,145,182] and general QoL,[109,113,117,121,183] but there have been inconsistent results

and patient-reported AF-specific QoL has rarely been explored.[111] A few exercise trials have shown positive results on AF symptoms. Malmo *et al*. (n=51 non-permanent AF, 18% females) reported statistically significant reductions in AF symptom frequency and severity following HIIT (Norwegian protocol: 4x4 min 85-95% HR_{peak}, 3x3 min 60-70% HR_{peak})[113] and Hegbom *et al*. (n=28 permanent AF, 7% females) following aerobic and strength training (70-90% HR_{peak}).[109] The latter found the greatest reductions in the frequency of *lack of energy*, and severity of *shortness of breath*.[109] Such improvements could translate to superior QoL and facilitate physical activity participation, teasing out possible mechanisms for the benefits of exercise training:[184] as patients improve their $\dot{V}O_{2peak}$ and become more tolerant of exertion following moderate- to vigorous-intensity exercise training, they may experience fewer symptoms of fatigue and dyspnea, and may feel more comfortable performing daily tasks, ultimately reporting better QoL. These associations are yet to be thoroughly explored.

Other exercise training programs have not led to reductions in AF symptoms. Bittman *et al*, enrolled patients with non-permanent AF (n=72, 39% females) in 4 months of home-based exercise training (target: 200 minutes/week), followed by 2 months of biweekly 60-minute supervised CR implementing interval training (2-minute work-bouts at 65-85% HR_{peak} interspersed with 2-minute rest periods at 60-65% HR_{peak} for 20 minutes). Such interventions did not improve AF symptoms or time spent in AF, but patients' general QoL increased more than in the usual care group.[183] Similarly, Reed *et al*. did not observe improvements in AF symptoms, yet self-reported measures of general QoL (i.e., physical functioning and physical health) significantly increased following 12 weeks of CR (ratings of perceived exertion [RPE]: 12-16 points, 40-85% HR reserve).[120] As opposed to Bittman and Reed, the exercise implemented by Malmo and Hegbom was predominantly in the vigorous-intensity range. Patients with AF may require a more targeted, intense exercise approach to counteract their poor health status at presentation and improve their AF symptoms.

Several studies in patients with AF have demonstrated the positive effects of exercise training on general QoL, including the physical functioning,[110,116,120,121,145,182] bodily pain,[110,121] general health perceptions,[113,116,121,182,183] vitality,[110,113,116,121,183] role limitations due to emotional problems,[110,121,183] role limitations due to physical health,[121,182] social functioning[121,182,183] and mental health[121] subscales of the Medical Outcomes Short Form (SF-36) questionnaire (all $p<0.05$). Clinically meaningful improvements in general QoL (≥5 point change in SF-36[185]) have also been shown in some studies implementing 40 to 75 minutes of moderate- to vigorous-intensity aerobic exercise training, 2 to 3 days per week, for 8 weeks to 6 months.[110,113,116,120,121,183] In contrast, others have not reported significant nor clinically relevant improvements,[108,119,121] particularly for the Mental Component Summary (MCS) score of the SF-36.[109,120] Further, the long-term benefits are unclear. CR programs of 3 to 6 months in duration led to significant improvements in general and AF-specific QoL from baseline to 3- and 6-months follow-up when compared to usual care.[111,183] Yet, no differences were found between groups at 12 months.[111,183] Methodological limitations (e.g., use of non-AF-specific QoL scales may not be sensitive to detect improvements, selection bias of fairly healthy individuals – see section 2.4.) may explain some of the inconsistencies.

Sex differences in patient-reported AF symptoms, QoL and exercise training

Females often report more frequent and severe AF symptoms,[72–74] and poorer QoL than males with AF.[75] No studies have compared differences in changes in AF symptoms following exercise training between sexes. The sparse sex-specific data available (n=1 RCT) suggest that CR may narrow the sex-disparity in QoL by being particularly beneficial for females.[67] Exercise-based CR (RPE: 13-17 points, 50-80% of HR_{peak}) increased AF-specific QoL as measured by the AF effect on quality-of-life (AFEQT) scale in females (global score: 48.8±18.6 to 83.2±15.1 points, $p=0.001$; treatment concern score: 63.4±27.3 to 80.4±19.7

points, p=0.004) but not males, when compared to usual care.[67] Such narrowing in sex differences may be related to the improved $\dot{V}O_{2peak}$ following exercise training. The lower $\dot{V}O_{2peak}$[67] in females may influence their greater symptoms of fatigue,[73,75,77] weakness[77] and dyspnea;[73] and poorer QoL[75] compared to males.

2.3.3. Additional mechanisms for the role of exercise in managing patients with atrial fibrillation

Emerging evidence supports that aerobic exercise training may simultaneously improve several CVD risk factors including blood pressure, resting HR, body mass index (BMI), and symptoms of anxiety and depression in patients with AF.[134,135,139] Whilst some sex-specific $\dot{V}O_{2peak}$ data are available, less is known about sex differences in the change in additional outcomes following exercise.[67] Thus, few sex-specific data are discussed in this section.

Hemodynamic measures: blood pressure and heart rate

Hypertension is the leading risk factor for AF, accounting for 22% of AF cases.[186] Chronic high blood pressure increases wall stress in the heart. To maintain the cardiac output, the heart experiences hypertrophy as a compensatory mechanism. Over time, maladaptive structural and electrical remodeling may occur.[187] Most (60 to 80%) patients with AF have high blood pressure,[29] and the prevalence is greater in females than males (75% vs. 68%;[74] 86% vs. 81%;[75] 63% vs. 41%[83]). Both hypertension and AF are associated with autonomic dysfunction and renin-angiotensin-aldosterone-system up-regulation, leading to increased circulating levels of angiotensin II and angiotensin converting enzyme, which, in turn, impair ion channel function and electrical function.[187] Despite being modifiable, high systolic blood pressure is a leading risk factor for age-standardized mortality in patients with AF,[13] and the percent contribution of high blood pressure to mortality is higher in females than males.[13]

Aerobic exercise training alone may not significantly reduce blood pressure in this population.[108,115,117,120,123,183] The prescription of antihypertensive medications in most of these patients leaves little room for improvement.[117,120,123] This contrasts with yoga programs[188] and aggressive exercise-based lifestyle interventions (e.g., combined strict blood pressure, body mass, lipid, glycemic and sleep-disordered breathing control) which led to significant reductions in systolic blood pressure (136 to 133 mmHg;[48] 161 to 127 mmHg, $p<0.001$),[47] even when the number of medications decreased. However, the long-term sustainability of such lifestyle changes remains doubtful.[65] Managing blood pressure through exercise may benefit females in particular. Females have a greater predisposition to hypertension[74,75,83] and proarrhythmogenic changes associated with hypertension. For instance, the LIFE study showed a greater prevalence of left atrial dilation (56% vs. 38%, $p<0.01$) and left ventricular hypertrophy (80% vs. 70%, $p<0.01$) in females than males with hypertension.[189,190] Such morphological changes in the heart are proarrhythmogenic.[191]

To compensate for the reduced stroke volume from asynchronous atrio-ventricular contractions, patients with AF experience faster resting and exercise HRs than their healthy peers.[123] Rate control in patients with AF aims to keep HR within a range that enables supplying the necessary cardiac output to match physiological demands and minimizes AF symptoms.[192] Tachycardia (HR ≥100 bpm) has been associated with symptomatic AF episodes.[193] Females' greater symptoms of palpitations[73,75,77,89] may arise from a greater autonomic dysfunction than males.[194,195] In support, females experience faster HRs during exercise[146] and AF (126±2 vs. 119±1;[87] 100±25 vs. 94±22 bpm[84]). Such sex difference arises from females' smaller cardiac size and their lower increase in ejection fraction during exercise: males rely predominantly on preload and the Frank-starling mechanism to increase cardiac output, while females depend somewhat more on an increase in HR because of their blunted sympathetic response (e.g., lower circulating catecholamines during exercise limit the

increase in vascular tone to enhance venous return, in turn, this impacts cardiac contractility).[146,152,153,167,168]

Several trials in patients with AF implementing HIIT or moderate- to vigorous-intensity continuous training (MICT) for a duration of 40 to 90 minutes, 2 to 3 days a week for 8 to 16 weeks have led to reductions in resting HR.[110,113,117,119,123,145] This improvement in autonomic function may be a result of an increase in vagal tone,[110] reduced sympathetic activation, and improved cardiac filling and contractility; in turn, allowing the heart to pump a greater amount of blood per beat.[196] This chronic HR reduction may be another avenue to narrow the gap in AF symptoms between sexes. In patients with AF (n=28, 7% females; n=51, 18% females),[110,113] exercising for 8 to 12 weeks led to reductions in resting HR (Δ: -7±14 bpm, p=0.002;[110] Δ: -3±6 bpm, p<0.05;[113] Δ: -9±20 bpm, p=0.049[117]), HR during exercise testing (Δ: -8%),[119] the severity and frequency of AF symptoms (p≤0.01)[109,110,113] and time in AF (Δ: -3.3%).[113] In addition, 9 to 11 weeks of CR have been shown to facilitate maintenance of sinus rhythm at 1-year follow-up (odds ratio: 1.77, 95% CI 1.02 to 3.05, p=0.042), without significant differences between sexes (odds ratio: F: 1.25 vs. M: 1.69).[49]

Anthropometric measures: body mass, waist circumference and body composition

An elevated BMI (overweight: ≥25, obesity: ≥30 kg/m^2), percent body fat and waist circumference are major risk factors for AF incidence[197,198] and progression.[31] High-risk waist circumference (F: ≥88 cm; M: ≥102 cm based on Caucasian populations)[124] is linked to growth and infiltration of epicardial fat in the atria[199] – a visceral adipose tissue with inflammatory and proarrhythmogenic properties. Obesity and high body fat perpetuate AF through several mechanisms.[31] For instance, left atrial enlargement is an independent predictor of AF and is present in most individuals with obesity.[199] Similar to the effects of hypertension, those with obesity experience a deleterious chronic increase in cardiac output:

the wall stress often fails to match the enlargement and hypertrophy of the heart chambers, predisposing them to systolic and diastolic dysfunction.[31] High body fat leads to fat infiltration in the atria, promoting electrical conduction heterogeneity through heightened autonomic dysfunction, atrial fibrosis and the release of inflammatory markers.[15,31]

The deleterious effects of obesity may be sex-specific. For instance, obesity is associated with a 64% increased risk of CVD in females and 46% in males.[200] Different body fat distribution predisposes males to develop greater abdominal obesity, yet a small increase in abdominal fat triggers a steeper rise in inflammation and arterial stiffness in females.[201,202] Further, females have a greater prevalence of obesity (50% vs. 37%;[77] 40% vs. 27%[84]), more epicardial adipose tissue,[203] a 10% higher body fat[204] and lower fat-free mass.[205] During menopause, the fat distribution shifts towards more visceral depositions; they are associated with sympathetic and renin-angiotensin-aldosterone-system upregulation and greater inflammation than subcutaneous fat.[206,207] These examples may impact clinical sex differences in patients with AF, such as females' greater development of atrial fibrosis.[104]

In patients with AF, 40 to 60 minutes of interval training 3 days a week for 12 weeks have been shown to significantly lower body mass[113] and fat.[116,117] However, other trials have not led to such improvements.[112,115,118,119,145] Similar to findings in hemodynamic measures, studies with the greater effects on anthropometrics implemented a more aggressive and holistic approach.[48,208] Sex-specific improvements in hemodynamic and anthropometric measures is an area to be explored, as no study to date has reported sex-specific blood pressure, HR or anthropometric changes following exercise training in patients with AF.

Mental health measures: anxiety and depression in patients with atrial fibrillation

Psychosocial factors such as a heightened depressive symptoms increase the risk of AF.[209] Elevated anxiety and depression scores are reported by one third of patients with AF,[210,211]

and are associated with worse AF symptoms[43,193,210,212] and QoL, even after a cardioversion or catheter ablation.[33,213] Patients with AF and poor mental heath: (i) report more severe AF symptoms regardless of device-measured AF burden;[214] (ii) are less likely to adhere to medications and healthy lifestyle behaviours;[215] (iii) utilize more healthcare resources;[216] and, (iv) are at a greater risk of mortality[217] than patients with better mental health.

The influence of exercise training on anxiety and depression should be investigated with a sex-specific lens. The mental health burden can be 2-fold higher in females than males,[218] which may influence their worse AF symptoms, QoL and prognosis.[73,74,219] Further, twice as many females than males have identified stress as the most frequent AF trigger.[77] Such symptoms may be reduced through exercise. For instance, chronic and acute exercise have been shown to lower cardiovascular reactivity to stress and anxiety sensitivity.[220–223] Studies examining the chronic effects of exercise training on mental health in adults with AF are very scarce. Some exercise programs implementing HIIT or MICT, 2 to 3 days a week, for 6 to 12 weeks led to significant improvements in mental health,[111,113,115] but this outcome remained unchanged in other studies.[110,120,121,183] Sex-specific data did not reveal improvements in depression, yet significant reductions in anxiety were found in males only (males: 5.7±3.8 to 3.9±3.4 points, p=0.01; females: 5.5±3.9 to 3.7±3.6 points, p=0.61) as measured by the hospital anxiety and depression scale (HADS) – likely due to the underrepresentation of females (59 females vs. 151 males).[67]

In summary, evolving knowledge sets the stage for the use of exercise training as an adjunct therapy in patients with AF due to its physical- and mental-health benefits, including potential improvements in $\dot{V}O_{2peak}$, patient-reported AF symptoms and QoL.[112,119,133–137,139] Yet, limitations of previous literature (e.g., lack of sex-based analyses, small single-centre RCTs) hamper the generalizability and clinical implications of research, the individualization of exercise training for this population, and the inclusion of exercise-based CR as part of

routine care for patients with AF.[65,224] Before discussing such gaps in section 2.4, we summarize debates on exercise prescription ranges for those with AF, and patient concerns regarding exercise-induced AF symptoms and episodes in the short-term.

2.3.4. Finding the most appropriate exercise prescription to maximize health outcomes in patients with atrial fibrillation

Aerobic exercise prescription is composed of four main principles (FITT): (1) Frequency: number of sessions per week; (2) Intensity: exertion during exercise; (3) Time: duration of each session or interval; and, (4) Type or mode of exercise.[124] The volume (frequency x intensity x time), progression or regression of the program, and rest periods influence the cardiorespiratory and peripheral responses to exercise training. Given its strong association with morbidity and mortality,[68,71] increasing $\dot{V}O_{2peak}$ is a main goal of exercise programs.[125] Designing exercise protocols where a high percentage of $\dot{V}O_{2peak}$ is maintained for a long duration has been shown to maximize $\dot{V}O_{2peak}$ improvements.[225–227] However, in clinical populations, patient preferences, fears, and their exercise and medical history should be considered through shared decision making to facilitate long-term physical activity participation.[228,229]

CR is a moderate-to-strong recommendation following most CVD interventions and diagnoses,[230] yet its role in managing patients with AF remains unclear.[224] Traditionally, MICT was the main exercise paradigm in CR. During MICT, patients use large muscle groups with aerobic machines at a constant intensity for a period of 20 to 60 minutes.[230] An alternative exercise paradigm for the general CVD population is HIIT, which intersperses brief (30 seconds to 4 minutes) work-bouts of higher-intensity exercise with lower-intensity or rest periods (30 seconds to 3 minutes).[230] There has been substantial scientific interest comparing the efficacy of HIIT with MICT. Meta-analyses in patients with CVD, including

heart failure, support that HIIT leads to similar or greater improvements in $\dot{V}O_{2peak}$ than MICT in a shorter amount of time.[231–234] Few trials have implemented HIIT in the AF population. A 12-week HIIT program in patients with non-permanent (n=51, 18% females) significantly improved $\dot{V}O_{2peak}$, AF symptoms and QoL.[113] Among the two trials in patients with AF comparing the impact of different exercise programming on health outcomes, no differences were observed.[122,145] Twelve weeks of biweekly 60-min sessions of low-intensity (RPE: 11-13 points) when compared to high-intensity (RPE: 16-18 points) exercise training led to comparable changes in $\dot{V}O_{2peak}$ (Low-intensity: 3.6±3.8 mL O_2/kg/min vs. High-intensity: 2.9±5.0 mL O_2/kg/min, p value not reported) in patients with non-permanent AF (n=70, 41% females).[122] The use of a subjective scale to prescribe and monitor exercise intensity is a limitation.[122] In line, no significant differences in improvements in functional capacity and general and disease-specific QoL were noted between 12 weeks of 23-minute biweekly HIIT compared to 60-minute MICT in patients with persistent and permanent AF (n=86, 34% females).[145] The latter result is promising as HIIT may overcome barriers that patients with AF, particularly females, may face to engage in exercise training, such as time constraints and lack of motivation.[235,236] The interval nature of HIIT may be more tolerable than continuous training for patients with AF who often report exercise intolerance.[237,238]

Disease-specific CR guidelines exist for several CVD conditions (e.g., heart failure peripheral artery disease).[230] AF-specific CR guidelines would be a step towards better precision medicine, as they consider the unique needs of the target population. Inconsistencies remain in exercise targets for those with AF.[65] For instance, the CCS/CHRS guidelines recommend patients engage in moderate-intensity aerobic exercise ≥30 min/day, ≥3 to 5 days/week, with a weekly target ≥200 minutes.[2] In contrast, others recommend 60 to 120 weekly minutes of moderate- to vigorous-intensity exercise training,[224] or 120 to 200 weekly minutes of aerobic and resistance training at ≤95% HR_{peak}.[137]

Clinical guidelines for patients with AF in Canada and Europe only recommend moderate-intensity exercise training.[2,36] This conservative approach may arise from the scarcity of HIIT studies in AF (only 3 trials, N=207 patients, of which 67 are females),[113,122,145] and the detrimental effects that *excessive* endurance training may have (e.g., excessive increase in vagal tone, atrial dilation).[239,240] Such deleterious effects, however, have only been observed following exceptionally high levels of vigorous endurance training (>5,000 MET-min/week), which are 5- to 10-fold the physical activity guidelines – an exercise volume rarely met by the general population.[240] The evidence to date seems too heterogeneous and scarce to establish optimal exercise ranges for health in patients with AF.[224,239] Nevertheless, the current focus on low- to moderate-intensity may represent a missed opportunity to further improve the health of patients with AF, and provide them with a diverse range of exercise options.

Another research gap is whether a specific exercise paradigm may maximize the health benefits for a given sex. As previously discussed, the notable clinical sex differences in patients with AF may warrant the consideration of sex when developing exercise recommendations.[65] Females with AF, who present with a worse CVD risk profile including a lower $\dot{V}O_{2peak}$,[67] may benefit from the greater cardiorespiratory and peripheral responses of higher-intensity exercise. However, their deconditioning, fears and preferences[74] towards exercise should be considered.

2.3.5. Short-term and acute responses to exercise in patients with atrial fibrillation

The emerging evidence on the chronic physical and mental health benefits of exercise training makes the high prevalence of insufficient physical activity in patients with AF concerning.[53] Patients with this complex cardiac arrhythmia experience unique barriers to

being physically active.[241,242] For instance, they report fears of exercise-induced AF symptoms and episodes.[241,242] To address this kinesiophobia (i.e., fear of movement),[243] more research clarifying the typical acute responses to exercise in patients with AF is needed. AF literature examining the short-term (e.g., within a week) or acute (e.g., during/within hours) effects of exercise on AF symptoms and other physiological and psychosocial markers is very limited. Our case series in males with permanent AF (n=4) revealed modest increases in HR and blood pressure during and following HIIT without adverse events or worsening symptoms such as chest pain or unusual dyspnea.[244] With larger and more representative (e.g., including females, several exercise paradigms) studies, we may show that the short-term and acute effects of exercise in patients with AF align with the responses of other CVD populations.[245–247] These findings could reassure patients that the presence of AF may not substantially alter the physiological response to exercise and/or worsen their clinical status.

There is a need to explore whether exercise impacts AF symptoms and episodes short-term in a sex-specific manner. On the one hand, higher HRs experienced by females with AF during an exercise bout[146] could lead to greater AF symptoms. On the other hand, physical activity may have a protective effect by reducing the risk of AF onset.[248] In support, a large prospective cohort study reported that a 1 h decrease in daily physical activity during the previous week increased the odds of AF onset the next day by 24%.[248] Clarifying the short-term effects of exercise would be valuable as patient concerns of exercise-induced AF symptoms and episodes are a barrier to exercise participation.[241,242] These investigations would be a first step to informing patients and healthcare providers of the typical exercise response in the AF population, which may ultimately facilitate exercise participation and prescription.

2.4. Research gaps and limitations of previous exercise trials in patients with atrial fibrillation

Limitations of previous studies (see Table 2.3.) contribute to the role of chronic (i.e., a 12-week exercise program) and short-term (i.e., weekly effects) exercise in patients with AF being less well-established when compared to other CVD conditions. In turn, this may be why an AF diagnosis is not a primary indication for CR referral.[2,36,240] To continue advancing the field of exercise and AF in a more equitable manner, sex should be considered when developing research trials.[65,224] Unfortunately, sex disaggregation of research findings remains infrequent.[94,193,249,250] Combined with the severe female under-representation in exercise research,[251,252] females may receive exercise recommendations without appropriate empirical scientific evidence. This dissertation work was designed considering some of the shortcomings summarized in Table 2.3. For instance, estimating $\dot{V}O_{2peak}$[149,156,253,254] has a greater measurement error and has been shown to limit our ability to detect sex differences, when compared to using direct $\dot{V}O_{2peak}$ measures with gas analysis.[149] The lack of device-measured physical activity data segregated by sex is also concerning, as self-reported physical activity is subject to recall and social desirability bias.[255] Few RCTs have measured AF-specific outcomes and report intervention adherence and fidelity. Additional examples are provided in Table 2.3. These knowledge gaps have formed the basis for this dissertation, as they may represent a missed opportunity to improve the care of a burgeoning patient population with a non-invasive, easily accessible adjunct therapy – exercise training.

Table 2.3. Main limitations of previous exercise trials in adults with atrial fibrillation.

Limitation	Impact
Relatively small sample size: n=10,[119] n=20,[114] n=28,[109,110] n=33,[115] n=43,[118] n=47,[116,117] n=51,[113] n=52,[111] n=61,[112] n=63,[123] n=70,[122] n=81,[183] n=86,[145] n=94,[120] n=96,[108] n=210[67]	Some trials might not have enough power to detect statistically significant differences in the measured outcomes. Few trials are multi-centre, limiting generalizability
Selection bias: highly symptomatic patients,[48,113,115] mostly asymptomatic with relatively good health,[109–112,119,120,122] sinus rhythm required at baseline[183]	Reduces the generalizability of results to the broader AF population
Study design: retrospective,[120,123,256] observational,[131,248] non-randomized[68,114,115,119,120,123]	Increases bias (e.g., selection, performance, reporting bias) and reduces the quality and generalizability of results
Highly variable instruments and methods of measurements: use of treadmill[68,113,183] vs. cycle ergometer;[108,114,117,119,121–123,145] use of estimated[108,110,111,117,119] vs. directly measured $\dot{V}O_{2peak}$; use of different scales (HADS,[120,121] HAM-D,[119] SF-36,[108,109,113,117,119–121,145,182,183] MLHF-Q,[117,182] PHQ-9,[111,115,183] GAD-7,[111,115,183] CCS-SAF,[183] Symptom severity checklist,[109,113] AFSS,[48,68,120,145,182,183] AFEQT[111,120])	Makes comparisons of findings between studies difficult Estimated $\dot{V}O_{2peak}$ has a greater measurement error Significant changes in AF-specific quality of life may not be detected if the tools used do not appropriately capture the specific psychosocial concerns of patients with AF
High heterogeneity between exercise interventions and underreporting of exercise prescription principles: length ranges from 6 to 52 weeks; frequency and duration of the exercise sessions from 2 to 5 days a week and 20 to 90 minutes; intensity and mode vary	Hampers reaching a clear consensus about exercise recommendations for AF as few studies implement the same exercise program, thus, there is little evidence supporting each exercise prescription
Inaccurate exercise intensity monitoring: Express exercise intensity as a percentage of peak heart rate[68,110,113,123,183] or a range of the Borg scale alone[108,117,122]	Heart rate may be an unreliable indicator of exercise intensity in patients with AF and the Borg scale is subjective. Both may hinder administering the right exercise dose
Underreporting of participants' adherence to the intervention and compliance with the exercise prescription[109,112,115,122]	A low adherence or compliance can hamper the benefits of exercise and sex differences in the response to exercise training
Lack of device measures of physical activity: few studies use accelerometers[108,113,132,183]	Is it unknow whether exercise trials enhance physical activity levels in those with AF
Underrepresentation of females with AF: <30% participants in exercise trials are females, despite 47% of patients with AF being females	Contributes to the knowledge gaps in AF in females. Most studies are underpowered to examine sex differences

AF: Atrial fibrillation; AFEQT: Atrial fibrillation effect on quality-of-life; AFSS: atrial fibrillation severity scale; CCS-SAF: Canadian cardiovascular society severity of atrial fibrillation scale; GAD-7: Generalized anxiety disorder; HADS: Hospital anxiety and depression scale; HAM-D: Hamilton depression rating scale; MLHFQ: Minnesota living with heart failure questionnaire; PHQ-9: patient-health questionnaire-9; SF-36: Medical outcomes short form questionnaire.

2.5. Research objectives and general hypotheses

Overall, this dissertation aims to provide novel insight into potential sex differences in the acute and chronic effects of exercise training on physical and mental health outcomes in patients with AF. The main purposes are divided in four research articles:

Study 1: Sex-based analyses of short-term effects and acute responses to exercise in patients with AF. The primary aim of this randomized cross-over study (Acute-AF trial) is to explore sex differences in short-term changes in self-reported AF symptoms when patients with symptomatic non-permanent AF engage in a week of exercise (i.e., 3 sessions of HIIT or MICT), compared to a Control week. It is hypothesized that females will experience greater symptom severity than males during the HIIT and MICT weeks, when compared to rest. Secondary aims will describe acute physiological and psychosocial exercise responses by sex.

Study 2: Sex differences on physical and mental health characteristics in patients with AF. For Study 2, I will leverage baseline data from two RCTs. The primary aim of this cross-sectional study is to compare $\dot{V}O_{2peak}$ between females and males with persistent and permanent AF. It is hypothesized that females will present with a lower $\dot{V}O_{2peak}$ than males. Secondary aims will compare AF symptoms, QoL and additional physical- and mental-health outcomes, including physical activity levels, between sexes.

Study 3: Sex-based analyses of the chronic effects of exercise training in patients with AF. For Study 3, I will use data from two RCTs. The primary purpose is to examine differences over time in $\dot{V}O_{2peak}$ between females and males with persistent and permanent AF following a 12-week exercise intervention (i.e., HIIT or MICT). It is hypothesized that females will improve their $\dot{V}O_{2peak}$ to a lesser extent than males following exercise training. Secondary aims will compare changes in AF symptoms, QoL and additional physical- and

mental-health outcomes, including physical activity levels, between sexes following exercise training.

Study 4: Systematic review of the effects of exercise training in patients with AF with a sex-based lens. The primary purpose of this systematic review is to pool data from previous studies to compare changes in $\dot{V}O_{2peak}$ following exercise training between females and males with any type of AF. It is hypothesized that females with AF will experience smaller improvements in $\dot{V}O_{2peak}$ than males following exercise training. Secondary aim will examine the impact of sex on changes in AF symptoms, AF-specific and general QoL, and additional physical and mental health outcomes (e.g., functional capacity, resting HR and blood pressure, BMI, anxiety and depressive symptoms, physical activity levels) following exercise training.

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CHAPTER 3 - Short-term effects and acute responses to exercise in females and males with non-permanent atrial fibrillation: the Acute-AF randomized crossover study

PREAMBLE TO STUDY 1

Chapter 3 focuses on sex-based analyses of potential short-term changes in symptoms when patients with atrial fibrillation (AF) engage in aerobic exercise training (i.e., 3 sessions of high-intensity interval training or 3 sessions of moderate-intensity continuous training) when compared to a week of rest. Patient concerns about experiencing an increase in AF symptoms with exercise guided the research questions for Study 1, as whilst they have been heard throughout the AF community, they have not been thoroughly examined with rigorous scientific methods. To inform patients and clinicians of the typical exercise responses in this population, Study 1 also describes sex-specific acute physiological and psychosocial responses to a bout of exercise.

3.1. Abstract

Background: Atrial fibrillation (AF) symptoms are common in patients with non-permanent AF, and they increase the risk for adverse events. Some data suggest reductions in AF symptoms following chronic (i.e., 8- to 12-week) exercise training (ET), yet the short-term (i.e., within days) and acute (i.e., during/following an exercise bout) responses to ET in patients with AF are misunderstood. **Aims:** To compare short-term changes in AF symptoms between females and males with symptomatic non-permanent AF when they engage in a week of high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT), compared to rest. Acute responses to ET were also described by sex. **Methods:** This was a repeated measures randomized counter-balanced study. Participants performed 3 x 25-minute HIIT (10x30s at 100% peak power output [PPO], interspersed with 10x30s at 25% PPO), 3 x 50-minute MICT (35 minutes at 60% PPO) on a cycle ergometer, and a Control non-ET week. Patients reported AF symptoms with a 7-day questionnaire during each study week (x3). Physiological (e.g., heart rate [HR] measured with a polar HR monitor, power output on the cycle ergometer, blood pressure) and psychosocial (e.g., perceived exertion using the 6 to 20-point Borg scale, affect using the Feeling Scale, anxiety using a visual analogue scale, enjoyment using the physical activity enjoyment scale) outcomes were measured during HIIT and MICT. Linear mixed-effects models with repeated measures were used to test the effects of the condition week, sex, and their interaction on symptom severity. **Results:** 6 females (35%) and 11 males (65%) enrolled in the ongoing Acute-AF study. The overall symptom score did not significantly differ across study conditions or sex. A condition-by-sex interaction was found, such that palpitation severity was lower during the HIIT than Control week in females. The enjoyment reported following HIIT and MICT did not differ between sexes. **Conclusions:** These preliminary results suggest that symptom severity may not be exacerbated in the short term by engaging in exercise training, yet additional analyses in a larger sample of patients with AF will provide more robust evidence.

3.2. Introduction

Atrial fibrillation (AF) is a burgeoning patient population.[1] AF can be broadly classified as non-permanent (i.e., *paroxysmal:* AF episode lasting between 30 seconds to 7 days; *persistent:* AF lasting beyond 7 days but <1 year; *longstanding persistent:* continuous AF for at least 1 year in patients for whom rhythm-control management is being pursued) or *permanent* (i.e., continuous AF for at least 1 year in patients who are not pursuing sinus rhythm restoration).[2] The irregular and rapid quivering of the atria during AF leads to burdensome symptoms in most (>70%) patients, including reduced exercise tolerance, palpitations and shortness of breath.[3] The development and persistence of AF symptoms are associated with worse psychological distress and quality of life (QoL), and a heightened risk for adverse events (i.e., stroke, worsening of heart failure) and hospitalization.[3–5] Thus, AF symptoms represent a therapeutic challenge as patients feel uninformed, unsupported and emotionally distressed about the acute and long-term health impacts of their symptoms.[6–8]

Some AF symptoms are more prevalent among patients with non-permanent AF.[9] In a cross-sectional survey (n=9,816, 44% females), a greater proportion of patients with non-permanent AF reported at least one AF symptom in the previous week, and more patients with non-permanent AF reported palpitations, when compared to those with permanent AF.[9] Despite the use of heart rhythm and rate control strategies (i.e., pharmacotherapy, electrical cardioversion, catheter ablation), up to 60% of patients remain symptomatic.[9] Further, females typically report greater frequency and severity of AF symptoms than males.[10–12]

Exercise training is recommended as an adjunct therapy for the management of patients with AF.[2,13] Exercising 40 to 75 minutes, three days a week for 8 to 12 weeks at a moderate- to vigorous-intensity has been shown to improve symptom frequency (Δ:-1.6±5.0; Δ:-4.4±5.3 points)[14,15] and severity (Δ:-1.5±4.0; Δ:5.4±6.1 points, all $p \leq 0.01$).[14,15] Although there have been several investigations on the chronic (e.g., an 8- to 12-week program) effects

of exercise training,[16–19] the short-term (e.g., within days) and acute (e.g., during and following an exercise bout) effects of exercise in patients with AF remain misunderstood.[20]

Patients with this complex cardiac arrhythmia face challenges in being physically active. Many report fear of exercise-induced AF symptoms and episodes.[6,21] Some worry that increasing their heart rate (HR) during exercise or overexerting themselves may beget an AF episode.[6,21] Our case series describing acute responses to high-intensity interval training (HIIT) in four males with permanent AF showed an increase in HR during supervised HIIT (range: +31 to +60 bpm), which decreased following cool-down (range: -22 to -67 bpm) without adverse events.[20] Changes in AF symptoms or psychosocial measures (e.g., affect, enjoyment) were not assessed, and data in females, those with non-permanent AF and across different exercise intensities are lacking.[20] Such research gaps merit examination as: (i) symptoms largely guide the decisions of the care of patients with AF;[2,13] (ii) enjoyment and other psychosocial measures influence long-term physical activity levels;[22–24] (iii) females represent 47% of patients with AF;[1] and, (iv) providing evidence on several AF subtypes and exercise protocols may serve to inform and reassure a broader group of patients with AF.

Fear of movement (i.e., kinesiophobia) is frequently observed in patients with AF.[25] Three months following a catheter ablation, more than 70% of patients (n=384, 40% female) reported a high score of kinesiophobia (>37 points based on the Tampa Scale for Kinesiophobia Heart).[25] Those who were more symptomatic reported greater kinesiophobia.[25] Scarce data in patients with heart failure suggest that this fear may be preceived as stronger with increasing exercise intensity.[26] Further, this fear may be sex-specific, as more females than males report symptoms of fear/anxiety,[27] and females experience faster HRs during exercise[28] and AF episodes.[29–31] Research addressing patient concerns regarding short-term effects and acute responses to exercise of different intensities with a sex-specific lens is warranted.[6,21,32]

The affective responses (e.g., feeling of pleasure/displeasure during exercise) to and enjoyment of exercise may predict future physical activity levels.[22–24] In the general population, improvements in mood/affect have been noted for several hours following a bout of exercise.[33] This may have positive implications for patients with AF, as negative emotions (e.g., sadness, anxiety, stress) have been linked to disease onset.[34] In support, in 95 patients with non-permanent AF who were in sinus rhythm at the time of enrolment, reporting happiness in a daily diary reduced the likelihood of experiencing an AF episode by 85% (as monitored by a Holter).[34] In contrast, feelings of stress and anger nearly doubled the risk of AF on the following day after adjustment for multiple variables.[34] Considering these associations, the patient concerns, and the knowledge gaps in short-term and acute responses to exercise in patients with AF, further work is needed for patients with AF who are symptomatic.[25]

3.3. Objectives and hypotheses

The primary aim of this study was to compare short-term changes in AF symptoms between females and males with symptomatic non-permanent AF when they engage in a standard week of aerobic exercise (i.e., 3 sessions of HIIT over 7 days, or 3 sessions of moderate-intensity continuous training [MICT] over 7 days) when compared to a Control week (i.e., no moderate to vigorous exercise over 7 days). We hypothesized that females would experience a more significant worsening in the overall symptom severity score than males during the HIIT and MICT weeks, when compared to rest. The secondary aim was to describe acute physiological (e.g., HR, power output, blood pressure) and psychosocial (perceived exertion, affect, anxiety, physical activity enjoyment) responses in each sex during HIIT and MICT.

3.4. Methods

Study design and setting

We used a repeated measures randomized counter-balanced design. All study visits occurred at the University of Ottawa Heart Institute (UOHI), a tertiary care cardiovascular centre located in Ontario, Canada. The trial was registered with ClinicalTrials.gov (NCT05085860), and was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines extended to randomized crossover trials.[35] The Sex and Gender Equity in Research (SAGER) guidelines were also considered for the reporting of sex and gender information.[36] Approval was obtained from the Ottawa Health Science Network Research Ethics Board (protocol #: 20210524-01H) and from the University of Ottawa (Health Sciences and Sciences Research Ethics Board, protocol #: H-12-22-8737).

Participants

Participants were recruited between January 2022 and January 2023 (this end date was selected given the student's timeline; recruitment for the Acute-AF study is ongoing). Main sources of patient recruitment included previous participation in a research study at the UOHI, referrals from healthcare providers, screening of the UOHI's electronic medical records, and community-level advertising through newspapers and flyers in the National Capital Region of Canada. All participants provided written, informed consent.

Eligible patients included those who: (1) had a documented diagnosis of paroxysmal or persistent AF; (2) were rate controlled with a resting HR ≤110 bpm; (3) were able to perform an incremental exercise test to volitional exhaustion (needed to determine the peak power output [PPO] for the exercise training prescription); (4) were ≥40 years old; (5) self-reported being symptomatic (≥2 AF symptoms in the past 4 weeks, see Appendix 3.1. for details); (6) if female, self-reported being postmenopausal according to the Stages of

Reproductive Aging Workshop (STRAW) criteria[37] (to enhance the homogeneity of the female group, as most females with AF are postmenopausal and sex hormones may impact conduction disturbances during AF episodes);[12,38,39] and, (7) were able to read and understand English or French.

Patients were excluded if they: (1) were participating in routine exercise training (>2x/week); (2) had unstable angina, uncontrolled diabetes mellitus, severe mitral or aortic stenosis, or hypertrophic obstructive cardiomyopathy with significant obstruction (this may interfere with the ability to engage in exercise training); (3) had an automated external defibrillator, an implantable cardioverter defibrillator or other types of pacemaker (as the use of KardiaMobile, a heart rhythm monitor device that was part of this trial, is not recommended); (4) were unable to access the Internet or a phone (iPhone and iPad required iOS version ≥ 10.0, Android required version ≥ 6.0) that connected to the Internet during the study period (needed to download the KardiaMobile app and capture ECG traces); or, (5) were unwilling or unable to complete the three conditions.

Study procedures

Screening and baseline visit

Research staff screened potentially eligible participants, and retrieved their sex (i.e., legal sex assigned at birth[40]), age and medical information from the UOHI's electronic medical records. During the baseline visit, patients underwent a medical assessment with a UOHI physician to confirm eligibility. Patients self-reported their prescribed medications and their current routine physical activity habits using a brief questionnaire (i.e., *Do you routinely engage in moderate- to vigorous-intensity physical activity? If Yes, how many days per week? If Yes, how many minutes per session?*). Patient sociodemographic and gender-related data were collected using the Genesis-praxy questionnaire, a self-report 28-item survey related to

the four main gender dimensions: gender identity, roles, relations and institutionalized gender (e.g., stress level, housework and caregiving responsibilities, education, income, employment status, social support, anxiety and depression severity).[41,42]

Hemodynamic and anthropometric measures

Resting HR and blood pressure were taken in a seated position during the baseline visit following standardized procedures[43] with an automated sphygmomanometer (Welch Allyn, Canada). Patients remained seated for 5 minutes prior to the measurement and were asked to keep their feet flat on the ground without crossing the legs. Research staff collected duplicate measurements and the average was reported.

Body mass was measured using a digital scale (Omron HBF-514C) to the nearest 0.1 kg, height was measured using a SECA 206 height measuring system to the nearest 0.1 cm, and waist circumference was measured at the midpoint between the lower costal margin and iliac crest while patients stood with arms at the sides, feet shoulder width apart and abdomen relaxed after a full exhalation[43] using a SECA 201 tape measure to the nearest 0.1 cm. Body Mass Index (BMI) was calculated based on the body mass and height (kg/m^2).

Body composition was measured once using a digital scale (Omron HBF-514C), which estimates percent body fat by hand-to-foot bioelectrical impedance analysis to the nearest 0.1%. Participants were given pre-testing guidelines for bioelectrical impedance testing,[44,45] including: (i) no eating or drinking for 4 h; (ii) no moderate- to vigorous-physical activity for 12 h; (iii) no alcohol consumption for 48 h; (iv) to void their bladder within 30 min; and, (v) to refrain from consuming caffeine and non-prescribed diuretics for 12 h. Participants were instructed to step barefoot on the scale, stand upright, hold the display unit with both hands and extend the arms parallel to the floor for 5-10 seconds. Body mass and percent body fat were then used to calculate fat-free mass (FFM=body mass - [body mass ×

% body fat / 100]). In healthy older adults (n=50, 66% female, 56 to 94 years old) the hand-to-foot and the foot-to-foot methods have shown high correlation (r=0.84, p<0.001) for percent body fat.[45] In healthy young adults, low-cost scales (e.g., Omron) have shown high correlation with air displacement plethysmography, a widely validated method for body composition assessment (r=0.97 to 0.98).[46]

Exercise test

During the baseline visit only, participants underwent an incremental cardiopulmonary exercise test (CPET) on an electronically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany). The test was supervised by certified study staff (e.g., Clinical Exercise Physiologists). Depending on each patient's physical activity habits, the protocol started with a 2-minute warm-up at 25W or 50W, and increased by 13W every minute until volitional exhaustion.[47] HR was monitored continuously using a 3-lead ECG. Ratings of perceived exertion (RPE) were recorded towards the end of every 1-minute stage using the 6-20 Borg scale[48] and blood pressure was manually measured every two minutes. Gas exchange was measured continuously with an Oxycon Mobile portable metabolic cart (Care Fusion, Yorba Linda, CA, United States). The highest 20-second average of oxygen uptake in mL O_2/kg/min represented their peak aerobic power ($\dot{V}O_{2peak}$). The highest power output (measured in Watts) achieved for at least 20 seconds was considered the PPO, and was used to determine the exercise prescription for each patient.

Randomization

For all participants, the order of the three experimental conditions (i.e., week of HIIT, MICT and non-exercise Control; see Figure 3.1.) was randomized virtually using REDCap (version 8.5.6., Vanderbilt University, US). A group external to the study, the UOHI Cardiovascular

Research Methods Centre, generated a random sequence stratified by sex (i.e., female or male) on a computer. The results were concealed until all baseline measures were completed. A 7-day wash-out period was included between each experimental week to minimize cumulative effects across conditions.[49]

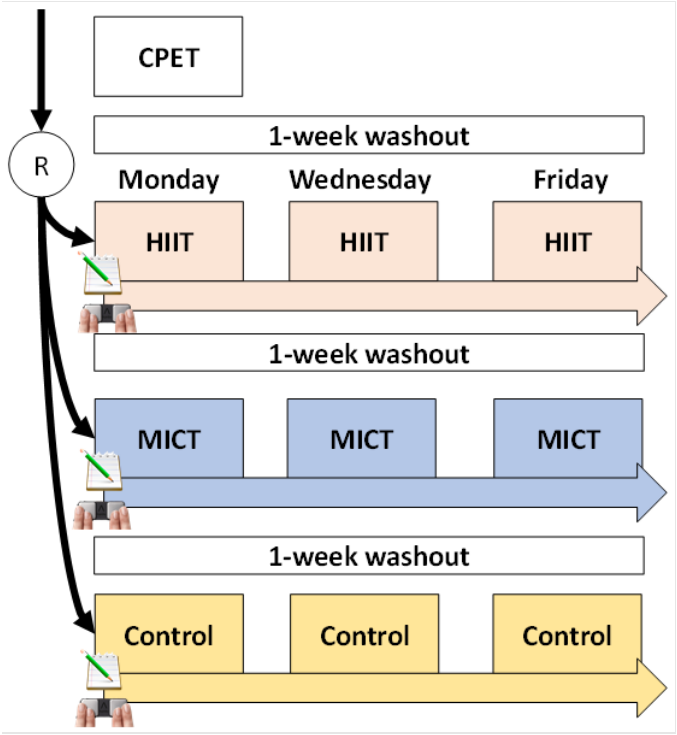


Figure 3.1. Experimental design of the Acute-AF study. Every Monday (x3), participants started to record AF symptoms on a 7-day AF symptom diary, and to record daily 30-second ECGs to monitor their heart rhythm. HIIT: high-intensity interval training; MICT: moderate-intensity continuous exercise, R: randomization.

Exercise conditions: week of HIIT and week of MICT

Exercise sessions were supervised one-on-one by research staff and conducted on an electronically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany) in the Exercise Physiology and Cardiovascular Health Lab at the UOHI. The exercise prescriptions for HIIT and MICT were designed to resemble a typical exercise week according to the World Health Organization physical activity guidelines for adults, which recommend engaging in at least 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity physical activity.[50]

High-intensity interval training (HIIT). Participants completed three sessions of HIIT over 7 days. Each session was 25 minutes in duration, including a 5-minute warm-up at 40% of PPO and a 10-minute cool-down at 25% PPO. The conditioning phase of the session was 10 minutes in duration; ten 30-second high-intensity work-bouts at 100% of PPO were interspersed with ten 30-second low-intensity work-bouts at 25% of PPO.

Moderate-intensity continuous training (MICT). Participants completed three sessions of MICT over 7 days. Each session was 50 minutes in duration, including a 5-minute warm-up at 40% of PPO and a 10-minute cool-down at 25% PPO. The conditioning phase of the session was 35 minutes in duration at 60% of PPO.

Control rest condition

Participants were asked to refrain from doing moderate- to vigorous-exercise training during the Control rest week. For any physical activity performed for at least 10 minutes, participants were asked to record the frequency, intensity, time, and type of activity in a log.

Outcome measures

Primary outcome

Symptoms of atrial fibrillation measured over 7 days in each condition week

The severity and duration of AF symptoms were measured prospectively using a patient-reported questionnaire (see Appendix 3.2.). Participants were asked to note the daily severity (0: not severe at all to 10: extremely severe) and duration (minutes) of AF symptoms, and the overall severity of all symptoms combined (0-10 scale). They were instructed to begin filling this 7-day questionnaire on the Monday of each experimental condition, and to record the symptoms daily to reduce the risk of recall bias. Since the daily assessment of AF symptoms was needed for this study, and available surveys only capture symptoms over the past four

weeks (beyond our assessment period),[51,52] a shorter version (7 days) of these questionnaires was developed by scientists and clinicians at the UOHI (Drs. Reed and Birnie).

Secondary outcomes

Mood measured over 7 days in each condition week

Mood was measured during each study condition since changes in this outcome could mediate changes in patient AF symptoms or episodes.[34] Using a shortened version of the Profile of Mood States[53,54] (POMS), respondents indicated the degree to which each adjective described themselves. The description was modified to: Please circle the number that best describes how you felt "today" (instead of "now"). The abbreviated POMS includes 40 items in the form of a Likert rating scale ranging from 0-Not at all to 4-Extremely. It evaluates seven aspects of mood: tension, depression, anger, vigor, fatigue, confusion, and esteem-related affect. The total mood disturbance, a composite summary score, was calculated by computing each aspect of mood and subtracting vigor and esteem-related affect. The weekly average total mood disturbance was calculated for each participant in each condition week; a constant (i.e., 100) was added to remove negative scores.[53,54] Higher total scores indicate higher levels of mood disturbance. The abbreviated POMS has good psychometric properties (Cronbach's α=0.67 to 0.93 in females following a myocardial infarction;[55] 0.66 to 0.95 in athletes[54]) and has shown to highly correlate with the original POMS (r=0.95).[55,56]

Status of the heart rhythm measured over 7 days in each condition week

The presence of sinus rhythm or AF was measured during the study conditions using a wireless KardiaMobile electrocardiograph (ECG) monitor (AliveCor, United States). This is a compact, portable device to record single-channel ECG rhythms by placing the index and middle fingers on the sensors for 30 seconds. Participants were instructed to record a 30-

second ECG trace once or twice (morning or evening) a day during each experimental condition. De-identified ECGs were electronically sent by patients or research staff. In patients of a tertiary cardiovascular care center (N=100, 34% females, 68±14 years old), the ability of KardiaMobile devices to detect AF has been shown to be non-inferior to a 12-lead ECG;[57] the sensitivity and specificity of KardiaMobile do detect sinus rhythm were 94% and 74%, respectively, and to detect AF they were 93% and 100%, respectively.

Acute measures during or following each exercise session

The variables measured before, during and following each exercise session are summarized in Table 3.1. During exercise, HR was measured with a HR monitor (Polar Ignite 2, © Polar Electro 2022, Kempele, Finland), the power output was noted by research staff, and blood pressure was measured manually with a sphygmomanometer and a stethoscope. Any unusual symptoms (e.g., dizziness, chest pain) or adverse events were reported by research staff.

Table 3.1. Measures and time points of data collection during the exercise sessions in the Acute-AF study.

Measure	Pre	Warm-up	Conditioning session**	Cool-down	Post
Heart rate	x	x	Every 30 s (HIIT) Every 5 min (MICT)	x	x
Power output			Every 30 s (HIIT) Every 5 min (MICT)		x
Blood pressure	x (automated)	x (manual)		x (manual)	x (automated)
Perceived exertion	x	x	Mid-point and end-point	x	x
Affective valence*	x	x	Every 1 min (HIIT) Every 5 min (MICT)	x	x
Anxiety levels	x				x
Enjoyment*					x

*Measured only during the Friday HIIT and MICT sessions. HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training.

Ratings of perceived exertion

Patients self-reported their RPE using the 6-20 Borg scale[48] after receiving standardized instructions on how to use it. This 15-grade scale includes both verbal anchors and numbers, ranging from 6-No exertion at all to 20-Maximal exertion. There are 9 verbal anchors: No exertion at all, extremely light, very light, light, somewhat hard, hard (heavy), very hard, extremely hard and maximal exertion.[48] The Borg scale is a valid tool for monitoring perceived exertion in healthy and CVD populations (N=2,560, 30% female, 66 [58 to 71] years old, n=146 with coronary artery disease), as it has shown to strongly correlate with HR ($r=0.74$, $p<0.001$) and blood lactate concentrations ($r=0.83$, $p<0.001$) during exercise.[58]

Affect fluctuations during exercise

Changes in affective valence (pleasure/displeasure) were recorded during the last HIIT and MICT sessions using the single-item Feeling Scale.[59] Participants rated their current feelings on an 11-point bipolar scale ranging from Very bad (-5) to Very good (+5).[59] There are verbal anchors at very good (+5), good (+3), fairly good (+1), neutral (0), fairly bad (-1), bad (-3), and very bad (-5). Participants received the following instructions: "While participating in exercise, it is common to experience changes in mood. Some individuals find exercise pleasurable, whereas others find it to be unpleasant. This feeling may fluctuate across time. That is, one might feel good and bad a number of times during exercise".[60] Higher scores denote greater levels of pleasure/affective valence. The Feeling Scale is a widely used scale to measure affect, and it moderately correlates with RPE ($r=-0.56$), although it has greater variability with increasing metabolic demands.[59]

Anxiety levels

To detect acute changes in anxiety, patients self-reported their anxiety levels using a 100-mm visual analogue scale anchored by "0 - completely calm and relaxed" on one end and "100 - as anxious and tense as I've ever been" on the other.

Enjoyment of the exercise session

Participants' enjoyment of the exercise sessions was measured using the Physical Activity Enjoyment Scale (PACES),[61] which was sent online via REDCap following the last HIIT and MICT sessions. One question from the original 18-item survey was removed given the timing of the survey ''I am very absorbed in the activity – I am not at all absorbed in the activity'. The instructions were also modified to "please think about the exercise you did today and rate your enjoyment of it".[60] The questions followed a 7-point bipolar rating scale (e.g., 1- "*I enjoy it*" on one end, to 7- "*I hate it*" on the other). Eleven items were reverse scored, leading to a total score out of 119 points. Higher scores denote greater enjoyment. The PACES has shown good interval validity (Cronbach's α=0.96[60,61]), although some researchers have suggested an 8-item PACES with better psychometric integrity for older adults.[62]

Sample size

Following guidelines to determine the sample size for pilot studies[63] and to incorporate sex-based analyses,[36] the total recruitment target was 20 participants (10 females and 10 males).

Statistical analyses

Statistical analyses were conducted using SPSS for Windows (v. 29; IBMCorp, Armonk, New York, US). Descriptive values are presented as means ± standard deviations for continuous variables. Categorical variables are presented as frequencies and percentages. To summarize the sample characteristics by sex, Independent t-tests and Mann-Whitney U tests

were used to compare the means of normally and non-normally distributed continuous variables, respectively, between females and males with AF. A missing value analysis of the primary measure (i.e., overall severity of AF symptoms) showed that the data were missing at random. A linear mixed-effects model for repeated measures using the full information maximum likelihood method to handle missing data[64] and unstructured covariate matrix was conducted to examine differences in patient AF symptom severity (primary outcome), with "condition week" and "sex" as fixed effects. The condition week (HIIT vs. MICT vs. Control), sex (female vs. male), and their interaction 'condition x sex' were included in the model. All residuals from the linear mixed-effects model were tested for normality using Kolmogorov-Smirnov tests. For residuals which were not normally distributed, a two-step approach using the Templeton Method was performed to transform these variables.[65] Because the transformed data showed consistent results with the original data, the latter are reported for descriptive purposes. The same approach was followed for the total mood disturbance (POMS) measure. Most acute measures are presented descriptively and in a graphical format given the small sample size to date. Enjoyment and the acute change in anxiety levels were compared using "HIIT vs. MICT" and "female vs. male" as fixed effects. Significance was set at $p<0.05$ (two-sided).

3.5. Results

A total of 6 females (35%) and 11 males (65%) enrolled in the Acute-AF study (see Figure 3.2). Of these, one male dropped out before completing the baseline exercise test due to testing-related anxiety leading to high blood pressure; and two participants did not begin the conditioning weeks due to caregiving responsibilities (n=1 female) and medical issues (n=1 male). One female completed the HIIT and Control week, but not the MICT week.

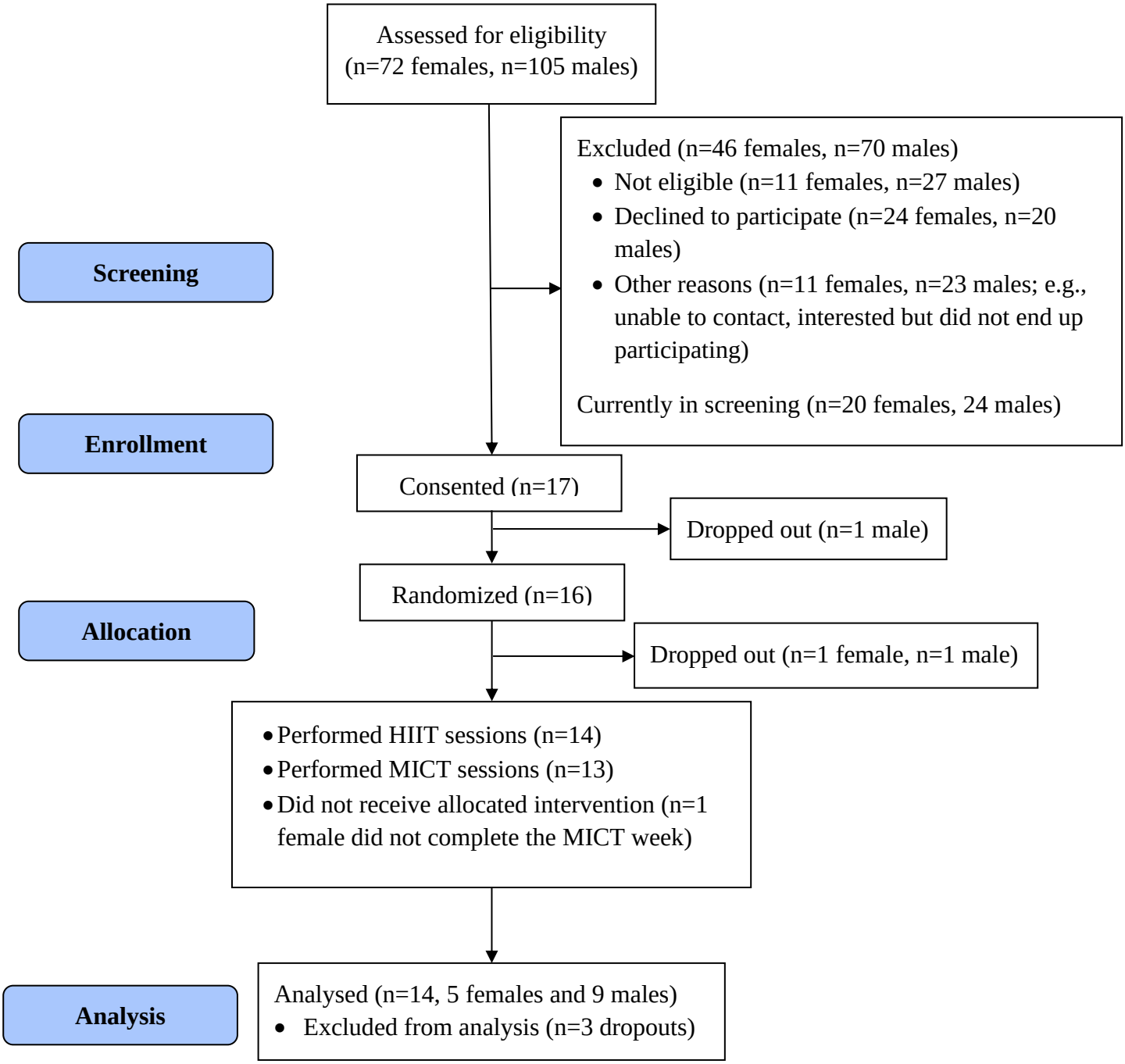


Figure 3.2. Flow diagram of participants recruited for the Acute-AF study.

All participants (n=15) who completed the Genesis-praxy identified as cis-gender (i.e., those who were assigned female sex at birth identified as women and those who were assigned male sex at birth identified as men). Participant sociodemographic and gender-related characteristics as reported by patients with the Genesis-praxy are summarized in Table 3.2. Given the small sample size, the sex-based analyses comparing baseline characteristics should be interpreted with caution. Most patients had persistent AF, were from North American or European origin, and had completed post-secondary school. Patient's mean stress was 4.4 points (scale 1 to 11). The reproductive status was late postmenopausal (Stage +2 as per STRAW criteria) in three females, and three females had undergone a hysterectomy. Females reported more caregiving responsibilities than males (e.g., F: 5.0±1.4 points, M: 0.8±1.8 points, p=0.033).

Patient AF symptoms reported during the enrolment process are summarized by sex in Table 3.2. More than one third of participants reported fatigue at rest and exercise intolerance during mild physical activity. A greater proportion of females (100%) than males (55%) reported palpitations (p=0.049).

Table 3.2. Participant sociodemographic and gender-related characteristics, and atrial fibrillation symptoms in patients with non-permanent atrial fibrillation.

	Females n=6	Males n=11	Total N=17	P between sexes
Sociodemographic and gender-related variables, n (%) or mean ± standard deviation				
Age (years)	66 ± 8	68 ± 7	67 ± 7	0.884
AF subtype				0.210
Persistent	4 (67)	10 (91)	14 (82)	
Paroxysmal	2 (33)	1 (9)	3 (18)	
Ethnicity: North American or European	5 (100)	7 (78)	12 (86)	0.568
Work status: Retired	1 (20)	5 (50)	6 (40)	0.264
Work status: Working	3 (60)	3 (30)	6 (40)	0.264
Education: Completed post-secondary school (college/university)	3 (60)	8 (80)	11 (73)	0.409
Primary person responsible for doing housework in the house	3 (60)	3 (30)	6 (40)	0.264
Primary earner in the house	1 (20)	6 (67)	7 (50)	0.094
Caregiving responsibilities (0-6 points)*	5.0 ± 1.4	0.8 ± 1.8	2.0 ± 2.6	**0.033**
Stress rating (1-11 points)	4.4 ± 2.3	4.3 ± 2.1	4.3 ± 2.1	0.933
Anxiety severity (0-21 points)	6.2 ± 4.2	6.5 ± 4.4	6.4 ± 4.2	0.901
Depression severity (0-21 points)	5.4 ± 2.7	5.8 ± 3.2	5.7 ± 2.9	0.813
Patient-reported AF symptoms in the previous 4 weeks, n (%)				
Palpitations	6 (100)	6 (55)	12 (71)	**0.049**
Exercise intolerance during mild physical activity	4 (67)	3 (27)	7 (41)	0.115
Weakness/fatigue at rest	1 (17)	6 (55)	7 (41)	0.129
Chest pain	3 (50)	2 (18)	5 (29)	0.169
Sweating	1 (17)	4 (36)	5 (29)	0.394
Dizziness	2 (33)	2 (18)	4 (24)	0.482
Agitation during AF	2 (33)	2 (18)	4 (24)	0.482
AF-related difficulty sleeping	2 (33)	2 (18)	4 (24)	0.482
Shortness of breath at rest	0 (0)	3 (27)	3 (18)	0.159
Nausea	1 (17)	2 (18)	3 (18)	0.938
Shortness of breath during mild physical activity	3 (50)	18 (7)	41 (10)	0.585

Data are presented as n (%) or mean ± standard deviation. P<0.05 denotes significance. *Question: If any of your children or other people living with you get sick, compared to their other parent, how likely is it that you will be the one to go get them (0=Very unlikely, 6=Very likely). The sociodemographic and gender-related variables were reported with the Genesis-praxy questionnaire. The AF symptoms were reported by patients during enrolment to confirm their eligibility (≥ 2 symptoms). AF: Atrial fibrillation.

The physical characteristics, cardiovascular disease (CVD) risk factors, medical history and medications are presented by sex in Table 3.3. All patients were non-smokers, and most had a high-risk waist circumference and an elevated BMI. The average $\dot{V}O_{2peak}$ was 19.1±8.6 mL O_2/kg/min in females and 20.2±6.8 mL O_2/kg/min in males (p=0.796). Resting diastolic blood pressure, height and FFM were lower in females than males (all $p<0.05$). Percent body fat was 13.7% higher in females than males (p=0.005). Four males had undergone a previous ablation and three males a cardioversion. Most (82%) patients were anticoagulated.

Table 3.3. Physical characteristics, medical history and medications by sex in patients with non-permanent atrial fibrillation.

	Females n=6	Males n=11	Total N=17	P between sexes
Hemodynamics and anthropometrics, mean ± standard deviation				
Resting heart rate (bpm)	64 ± 18	70 ± 9	68 ± 12	0.381
Resting systolic blood pressure (mmHg)	120 ± 20	141 ± 18	133 ± 21	0.062
Resting diastolic blood pressure (mmHg)	75 ± 13	86 ± 9	82 ± 12	**0.047**
Height (cm)	170.3 ± 7.0	183.6 ± 5.7	178.9 ± 8.9	**0.001**
Body mass (kg)	82.8 ± 21.4	98.4 ± 10.1	92.9 ± 16.3	0.140
Body mass index (kg/m^2)	29.0 ± 8.7	29.2 ± 2.2	29.1 ± 5.2	0.958
Body fat (%)	40.6 ± 11.1	26.9 ± 3.0	31.7 ± 9.5	**0.005**
FFM (kg)	25.2 ± 4.3	31.7 ± 1.5	29.4 ± 4.2	**0.002**
Waist circumference (cm)	97.8 ± 16.4	110.0 ± 8.4	105.6 ± 12.8	0.138
Peak aerobic power (mL/kg/min)*	19.1 ± 8.6	20.2 ± 6.8	19.7 ± 7.3	0.796
Peak aerobic power (mL/kg FFM/min)*	32.0 ± 8.9	27.5 ± 9.2	29.6 ± 9.0	0.388
Peak aerobic power (L/min)*	1.52 ± 0.48	1.98 ± 0.65	1.77 ± 0.6	0.180
Peak power output (W)	118 ± 43	157 ± 49	142 ± 50	0.132
Cardiovascular disease risk factors, previous medical conditions and procedures, n (%)				
Non-smoker	6 (100)	11 (100)	17 (100)	-
Elevated body mass index	3 (50)	10 (91)	13 (77)	0.127
High-risk waist circumference	4 (67)	9 (82)	13 (77)	0.482
Hypertension	1 (17)	7 (64)	8 (47)	0.064
Obstructive sleep apnea	2 (33)	5 (46)	7 (41)	0.627
Dyslipidemia	1 (17)	5 (46)	6 (35)	0.235
Coronary artery disease	0 (0)	3 (27)	3 (18)	0.159
TIA or stroke	2 (33)	1 (9)	3 (18)	0.210
Diabetes	0 (0)	2 (18)	2 (12)	0.266
Myocardial infarction	0 (0)	1 (9)	1 (6)	0.446
Peripheral vascular disease	0 (0)	1 (9)	1 (6)	0.446
Ablation	0 (0)	4 (36)	4 (24)	0.091
Cardioversion	0 (0)	3 (27)	3 (18)	0.159
Percutaneous coronary intervention	0 (0)	1 (9)	1 (6)	0.446
Medications, n (%)				
Anti-coagulant	4 (67)	10 (91)	14 (82)	0.210
β-blocker	1 (17)	7 (64)	8 (47)	0.064
Statin	1 (17)	6 (55)	7 (41)	0.129
Angiotensin II receptor blocker	0 (0)	4 (36)	4 (24)	0.091
ACE-inhibitor	1 (17)	2 (18)	3 (18)	0.938
Diuretic	0 (0)	3 (27)	3 (18)	0.159
Hormone replacement medication	2 (33)	0 (0)	2 (12)	**0.041**
Calcium-channel blocker	0 (0)	2 (18)	2 (12)	0.266
Anti-depressant	1 (17)	1 (9)	2 (12)	0.643
Anti-arrhythmic	0 (0)	2 (18)	2 (12)	0.266
Glucose control	0 (0)	1 (9)	1 (6)	0.446
Anti-platelet	1 (17)	0 (0)	1 (6)	0.163

Data are presented as n (%) or mean ± standard deviation. P<0.05 denotes significance. ACE: Angiotensin-converting enzyme; TIA: transient ischemic attack. *Gas analyses data to measure peak aerobic power were available in 13 participants (6 females, 7 males). FFM: Fat-free mass.

Primary outcome: Short-term changes in patient symptoms of atrial fibrillation

A total of 13 participants (5 females, 8 males) returned the 7-day AF symptom diaries. Participants were generally low symptomatic, with a mean severity score of 2.5 ± 1.7 points in females and 1.1 ± 1.4 points in males (the scale ranges from 0 to 10). Main effects of the condition week (i.e., HIIT, MICT, Control), sex (i.e., female or male) and their interaction are shown in Table 3.4. The overall symptom severity did not differ across study conditions or sex, yet a condition-by-sex interaction was found, such that palpitation severity was significantly lower during the HIIT than Control week in females, but not males (see Figure 3.3.). Data on the duration of each symptom was not analyzed since several participants did not complete this section (see Appendix 3.3.).

Table 3.4. Severity of atrial fibrillation symptoms by conditioning week and sex in patients with non-permanent atrial fibrillation.

		HIIT (n=4 F, 7 M)	**MICT (n=4 F, 8 M)**	**Control (n=5 F, 7 M)**	**Condition effect**	**Sex effect**	**Condition *sex**
Overall symptom severity	F	2.3 ± 1.6	2.3 ± 1.9	2.9 ± 2.1	0.206	0.107	0.441
	M	0.7 ± 0.7	1.2 ± 1.5	1.4 ± 1.9			
Palpitations severity	F	2.5 ± 1.8	2.5 ± 2.1	2.8 ± 1.8	**0.024**	0.067	**0.021**
	M	0.4 ± 0.8	0.6 ± 1.8	1.1 ± 2.0			
Dyspnea severity	F	0.4 ± 0.8	0.0 ± 0.1	0.2 ± 0.4	0.075	0.797	0.980
	M	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5			
Fatigue severity	F	1.2 ± 1.6	1.0 ± 1.3	1.2 ± 1.4	0.344	0.871	0.966
	M	0.7 ± 1.1	1.3 ± 2.2	1.1 ± 2.0			
Dizziness severity	F	0.7 ± 1.4	0.3 ± 0.5	0.1 ± 0.1	0.369	0.342	0.343
	M	0.1 ± 0.3	0.3 ± 0.5	0.2 ± 0.4			
Difficulty sleeping severity	F	0.5 ± 0.7	0.4 ± 0.5	0.6 ± 0.9	0.954	0.350	0.236
	M	1.3 ± 2.0	1.3 ± 2.5	1.3 ± 2.3			
Anxiety or agitation severity	F	1.0 ± 0.8	1.2 ± 1.5	1.2 ± 1.1	0.415	0.290	0.368
	M	0.9 ± 1.9	0.5 ± 1.0	0.1 ± 0.9			

Data are presented as mean ± standard deviation. P<0.05 denotes significance. F: Females; HIIT: High-intensity interval training; M: Males; MICT: Moderate-intensity continuous training. Participants did not experience symptoms of nausea or sweating.

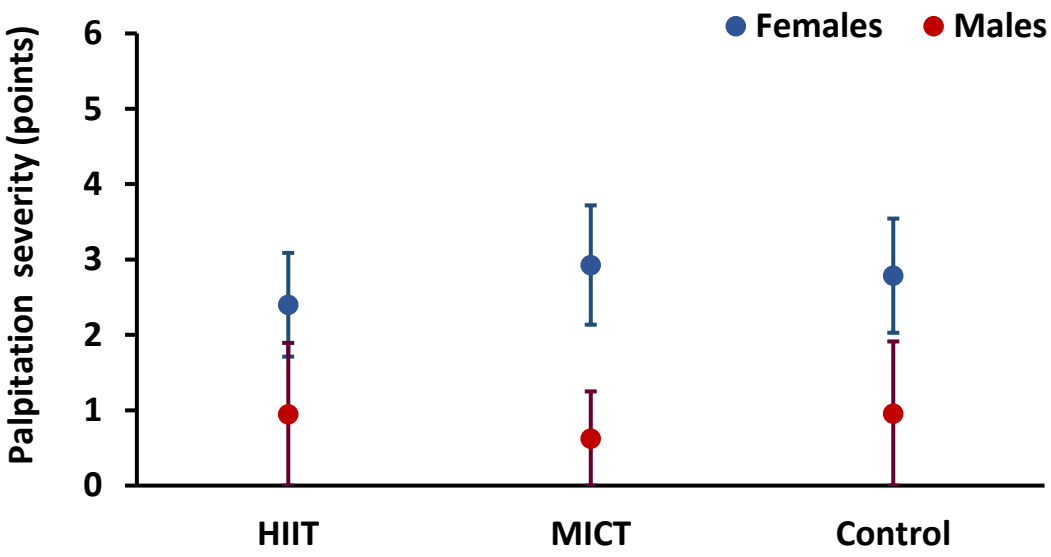


Figure 3.3. Palpitation severity in females and males with non-permanent atrial fibrillation during the week of High-intensity interval training, Moderate-intensity continuous training and Control. Data presented as estimated marginal means and standard errors from the linear mixed-effects model. HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training.

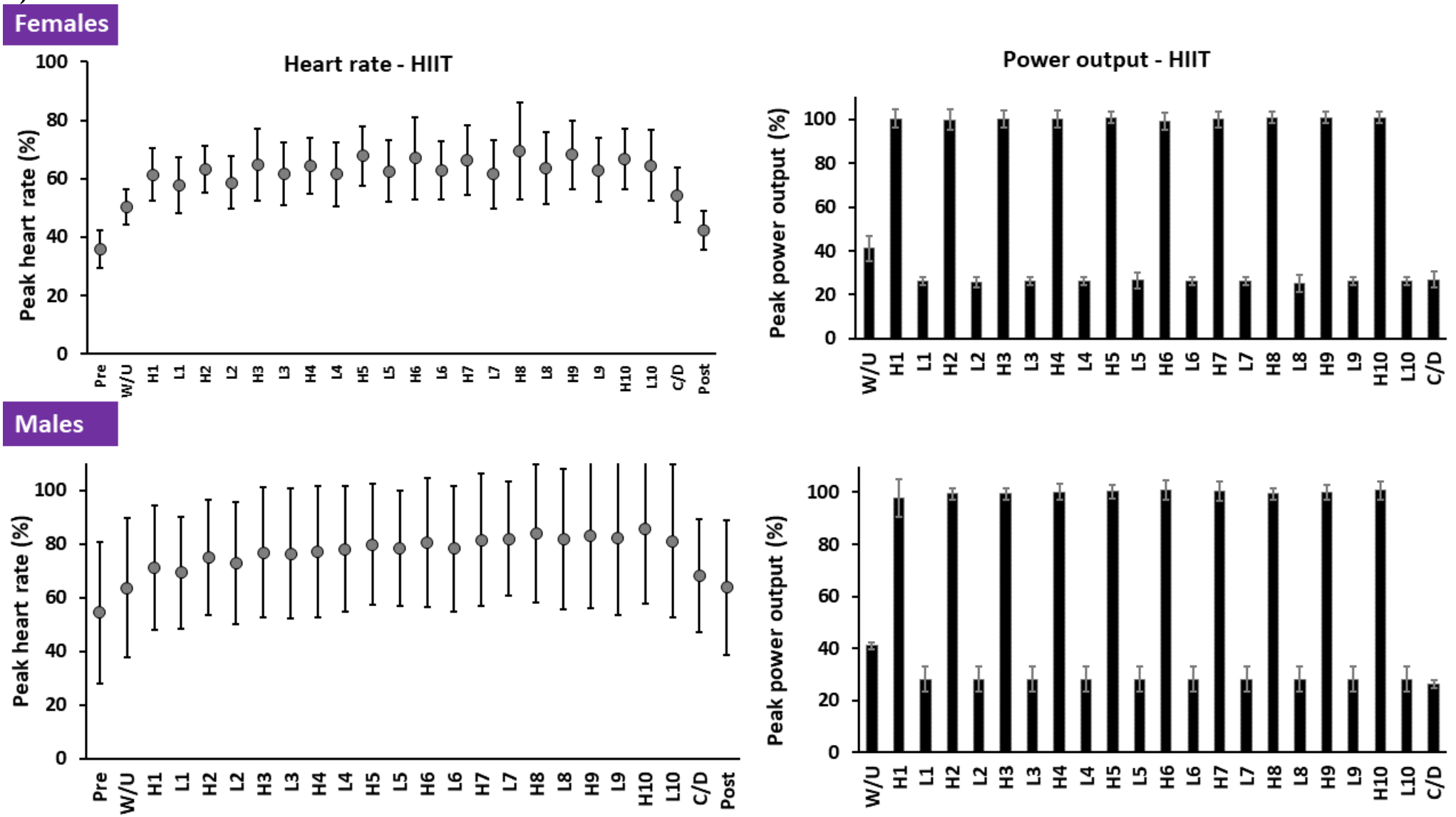
Secondary measures

Mood. Complete POMS data were available from 10, 12 and 12 participants for the HIIT, MICT and Control week, respectively. No differences in mood were found across conditions (F=0.457, p=0.644) or sexes (F=0.360, p=0.559); and no significant interaction was observed (F=2.471, p=0.126). In females, the mean total mood disturbance was 92.0±7.5 points, 89.9±10.6 points and 95.7±6.6 points during the HIIT, MICT and Control weeks, respectively. In males, the mean total mood disturbance was 101.5±34.8 points, 98.7±32.9 points and 98.5±27.9 points during the HIIT, MICT and Control weeks, respectively.

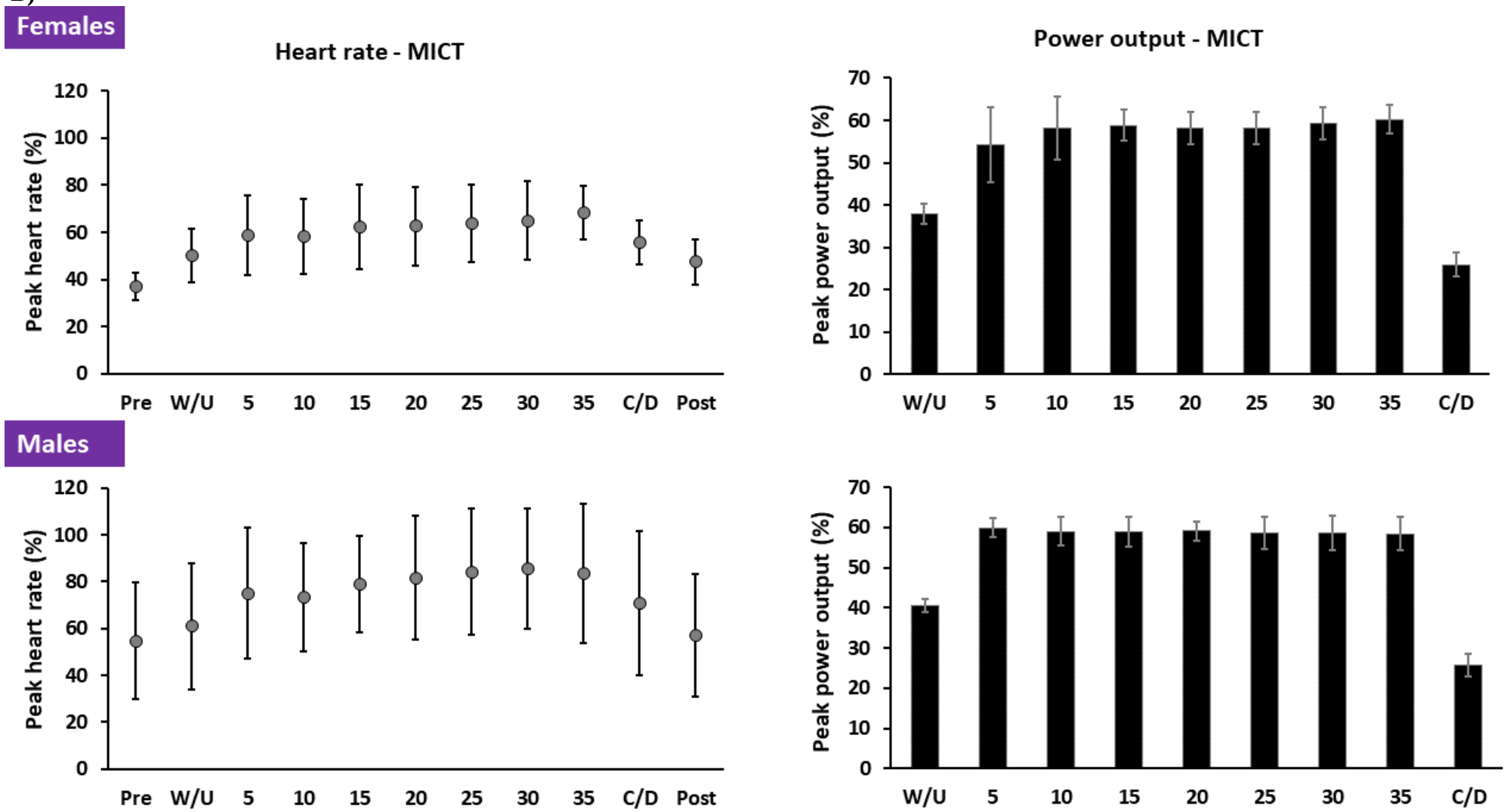
Status of the heart rhythm. We received ECGs recorded with the KardiaMobile from 14 participants. Of these, ECGs from the three study conditions were available in four females and seven males. Thus, these data are summarized descriptively. Two females and five males were always in AF, whereas two males were always in sinus rhythm during the three study conditions. The ECGs of two females showed AF some of the time (HIIT: 4 of the 12 ECGs recorded showed AF; 2 of the 14 ECGs recorded showed AF; MICT: 5 of the 12 ECGs recorded showed AF and 4 of the 10 ECGs recorded showed AF, Control: 3/12 and 3/18 ECGs showed AF).

Acute responses to exercise training. The acute responses to HIIT and MICT are shown by sex in Figure 3.4. (A-D). Given the small sample size for the acute measures (HIIT: 5 F, 9 M; MICT: 4 F, 9 M), such responses are presented mostly descriptively. The % HR and power output during the exercise sessions of all patients were averaged. Based on a visual inspection of the graphs, males experienced greater variability in HR than females. Both sexes complied with the exercise prescription. During HIIT, the mean percent PPO was 100±1% for the work bouts (100% prescribed) and 26±1% for the active recovery bouts (25% prescribed) in both sexes, whereas during MICT it was 58±2% in females and 59±1% in males (60% prescribed). RPE and blood pressure values from each participant are presented in Figure 3.4. as the average of the three exercise sessions. A visual inspection of the graphs shows moderate increases in systolic blood pressure during exercise, which returned close to resting values with cool-down. The average session RPE in HIIT was 12.9±1.0 points in females and 13.3±1.2 points in males. For MICT, it was 13.2±0.9 points in females and 13.1±1.4 points in males. Main effects of time showed increases in RPE during exercise (HIIT: $F=90.082$, $p<0.001$; MICT: $F=27.827$, $p<0.001$) without sex effects or interactions.

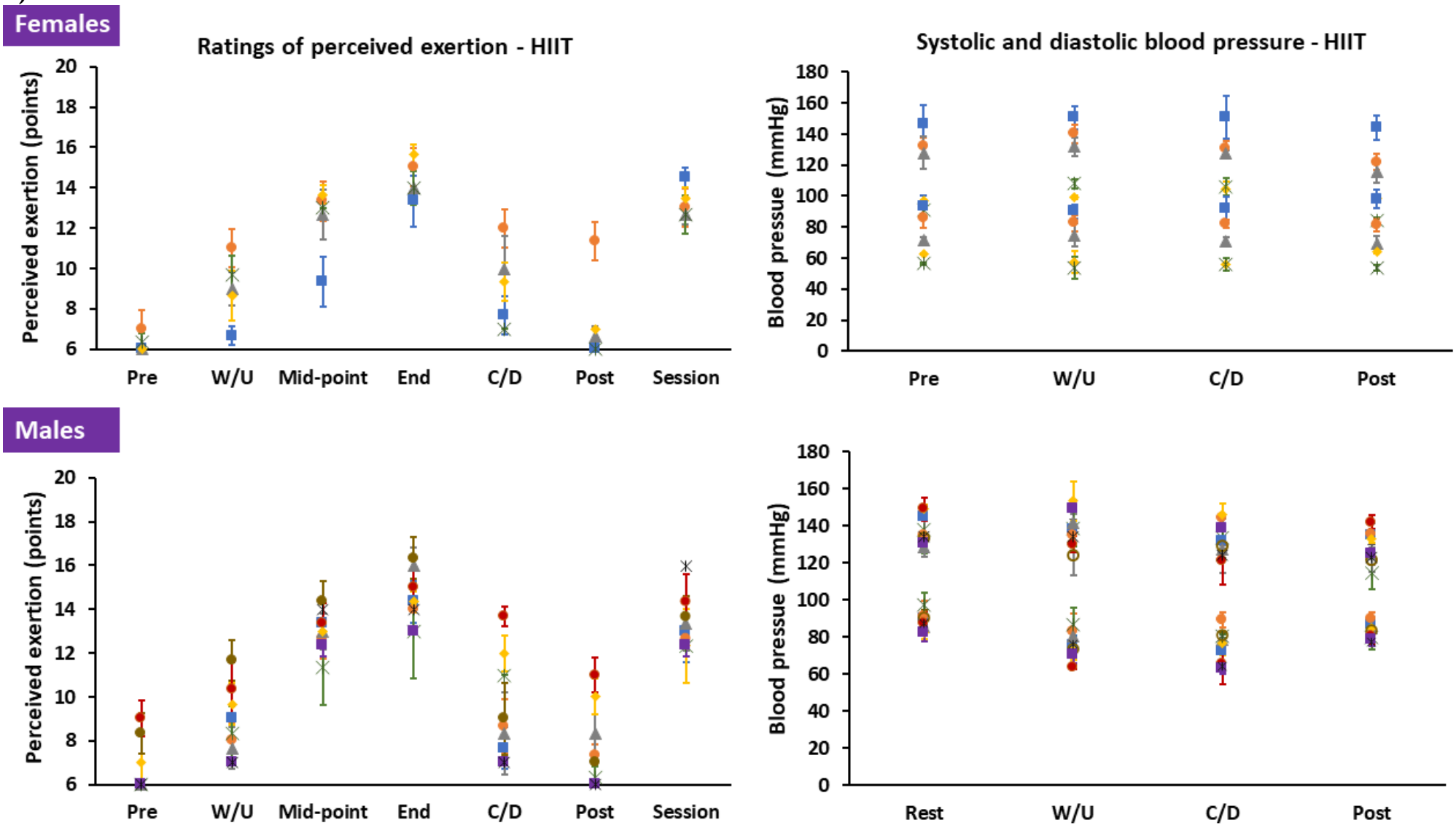
A)


Females
Heart rate - HIIT
Peak heart rate (%)
Pre
W/U
H1
L1
H2
L2
H3
L3
H4
L4
H5
L5
H6
L6
H7
L7
H8
L8
H9
L9
H10
L10
C/D
Post
Power output - HIIT
Peak power output (%)
Males

B)


Females
Heart rate - MICT
Peak heart rate (%)
120
100
80
60
40
20
0
Pre
W/U
5
10
15
20
25
30
35
C/D
Post
Power output - MICT
Peak power output (%)
70
60
50
40
30
20
10
0
W/U
5
10
15
20
25
30
35
C/D
Males
Peak heart rate (%)
Pre
W/U
5
10
15
20
25
30
35
C/D
Post
Peak power output (%)
W/U
5
10
15
20
25
30
35
C/D

C)


Females
Ratings of perceived exertion - HIIT
Perceived exertion (points)
20
18
16
14
12
10
8
6
Pre
W/U
Mid-point
End
C/D
Post
Session
Systolic and diastolic blood pressure - HIIT
Blood pressue (mmHg)
180
160
140
120
100
80
60
40
20
0
Pre
W/U
C/D
Post
Males
Perceived exertion (points)
Pre
W/U
Mid-point
End
C/D
Post
Session
Blood pressue (mmHg)
Rest
W/U
C/D
Post

D)

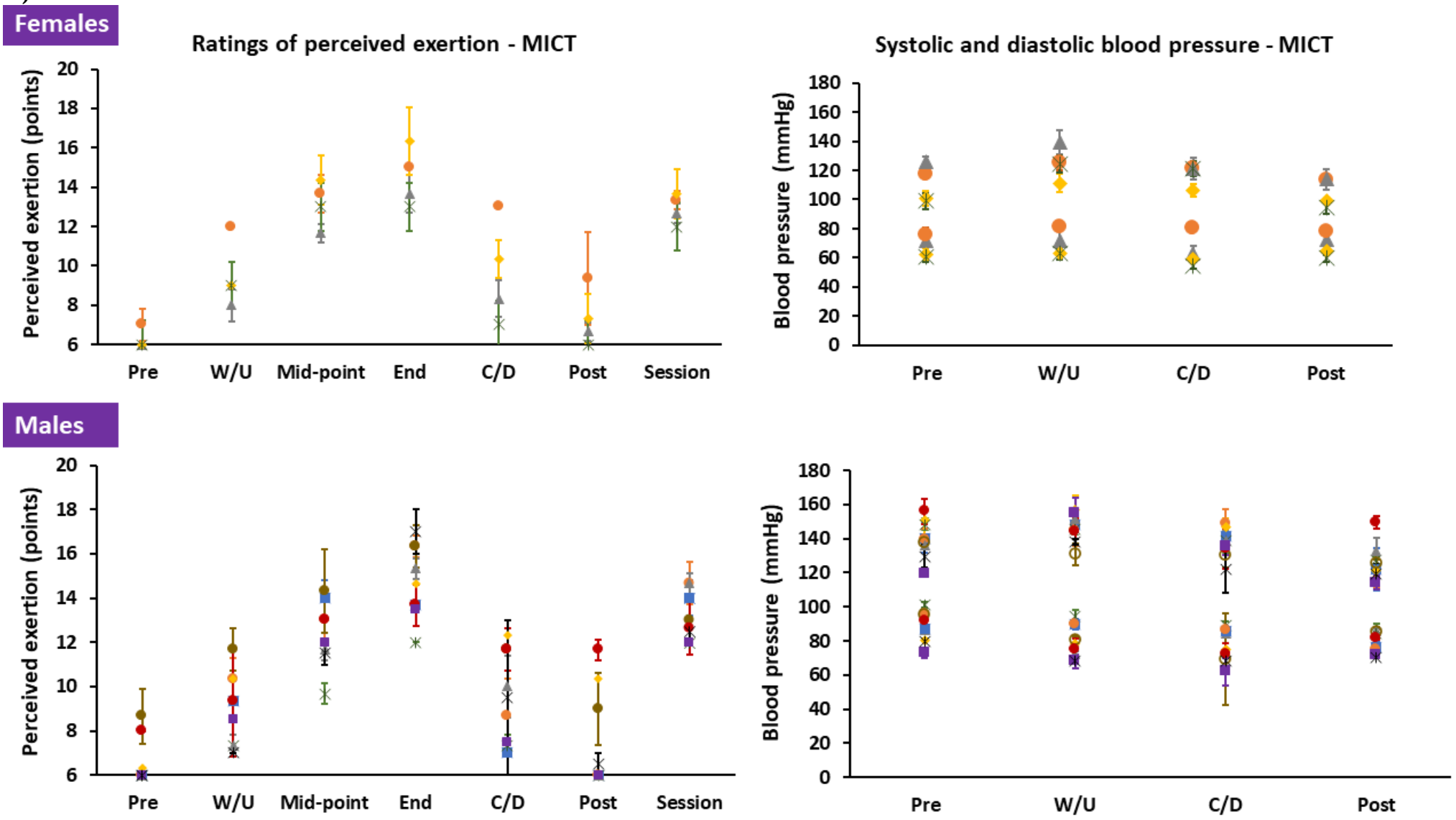

Females
Ratings of perceived exertion - MICT
Perceived exertion (points)
20
18
16
14
12
10
8
6
Pre
W/U
Mid-point
End
C/D
Post
Session
Systolic and diastolic blood pressure - MICT
Blood pressure (mmHg)
180
160
140
120
100
80
60
40
20
0
Pre
W/U
C/D
Post
Males
Perceived exertion (points)
20
18
16
14
12
10
8
6
Pre
W/U
Mid-point
End
C/D
Post
Session
Blood pressure (mmHg)
180
160
140
120
100
80
60
40
20
0
Pre
W/U
C/D
Post

Figure 3.4. Acute responses to high-intensity interval training and moderate-intensity continuous training by sex in patients with non-permanent atrial fibrillation. Values are plotted as means and standard deviations. Descriptive data are presented as the average percent heart rate and power output across all participants during HIIT (A) and MICT (B), and as the individual average ratings of perceived exertion and blood pressure of each participant across the three HIIT (C) and MICT (D) sessions. In instances when participants reported the same values for the three exercise sessions, the standard deviation was not plotted (as it was 0, e.g. some perceived exertion values). The available N for the acute measures was: HIIT: 5 females, 9 males; MICT: 4 females, 9 males. C/D: Cool-down; H: High-intensity work bout; HIIT: High-intensity interval training; L: Active recovery bout; MICT: Moderate-intensity continuous training; PO: Power output; W/U: Warm-up.

Acute changes in affect are presented descriptively. Each participant's affective valence during Friday's HIIT and MICT sessions are shown by sex in Figure 3.5. Participants reported their anxiety levels before and following each bout of exercise. A significant effect was found ($F=27.801$, $p<0.001$), such that the anxiety change score decreased following HIIT (-3.5±18.2 points) and increased following MICT (4.6±17.1 points), without a sex effect ($F=0.010$, $p=0.922$) or an interaction ($F=2.153$, $p=0.166$).

The mean enjoyment score as measured by the PACES following HIIT and MICT was 90.2±10.6 points and 87.3±24.3 points in females, respectively, and 97.3±13.0 and 95.6±13.9 points in males. Enjoyment did not differ between HIIT and MICT ($F=0.127$, $p=0.729$) or sexes ($F=0.736$, $p=0.406$). No interaction was found in the PACES score ($F=0.019$, $p=0.894$)

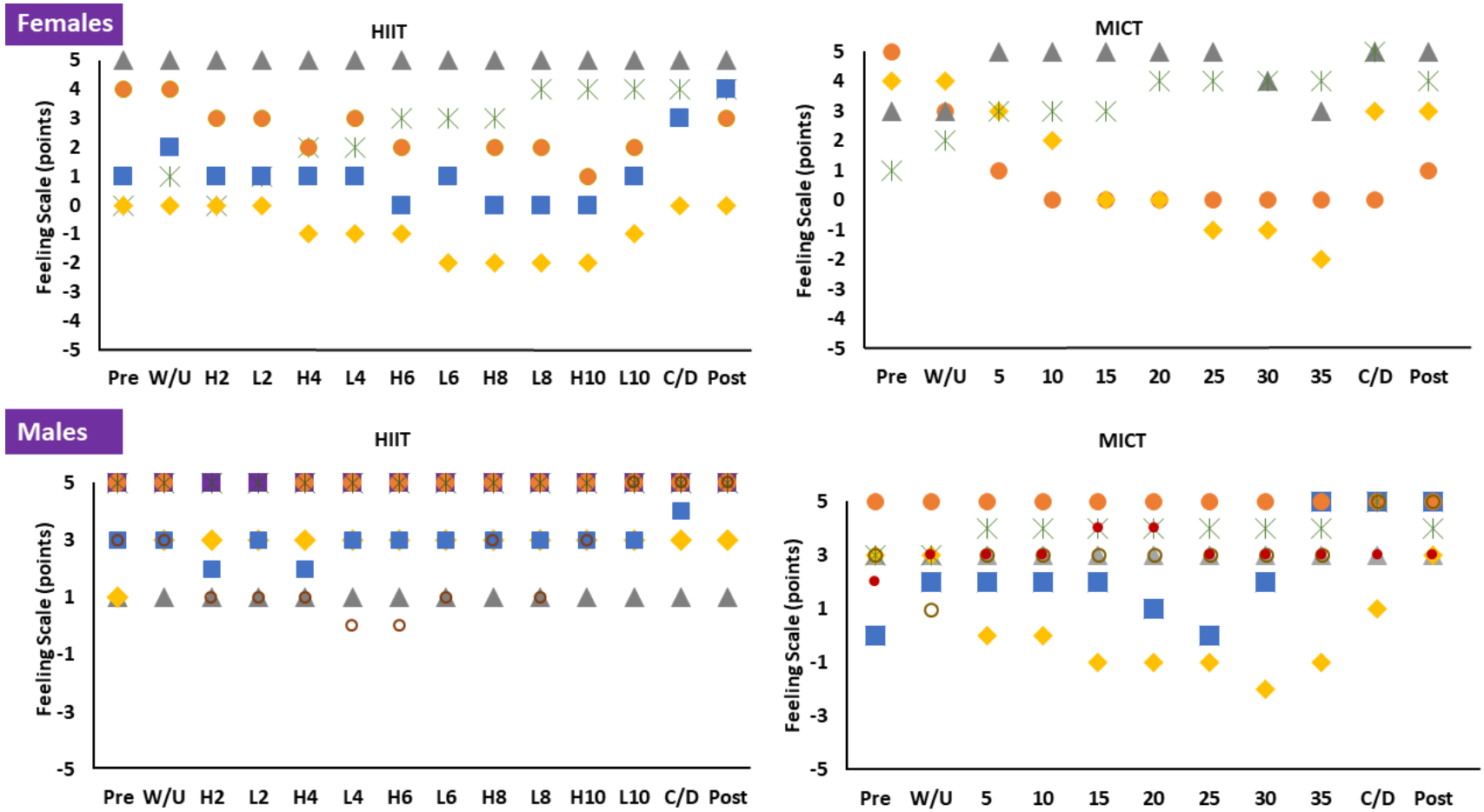


Figure 3.5. Affective valence as measured by the Feeling Scale in females and males with non-permanent atrial fibrillation during one high-intensity interval training and one moderate-intensity continuous training session. Individual participant values are plotted for descriptive purposes. The available N for the affective measures was: HIIT: 5 females, 7 males; MICT: 4 females, 7 males. C/D: cool-down; H: Work bout; HIIT: High-intensity interval training; L: Active recovery bout; MICT: Moderate-intensity continuous training; W/U: Warm-up.

3.6. Discussion

Patient fears of exercise-induced AF symptoms and episodes have been cited as barriers to exercise participation throughout the AF community,[1-3] yet they have not been thoroughly examined. Patients and clinicians have been calling for acute exercise studies to understand the typical exercise responses more thoroughly in patients with AF.[20,21,66] The Acute-AF study compared differences in patient-reported AF symptom severity across three study conditions (i.e., a week of HIIT, MICT and non-exercise control) between females and males with symptomatic non-permanent AF. Contrary to our hypothesis, no differences were observed in the overall symptom severity score across conditions between sexes. We found a condition-by-sex interaction, such that the severity of palpitations was lower during the week of HIIT than control in females, but not males.

Primary outcome: Short-term changes in patient AF symptom severity. Patients with AF worry about worsening of AF symptoms during or following a bout of exercise.[1-3] Such concerns are important as symptoms largely guide the clinical decisions of care in patients with AF,[2,13] and are a main reason for patients to seek medical attention.[8] Further, kinesiophobia may discourage participants from engaging in regular physical activity, which is concerning as a lower cardiorespiratory fitness may then exacerbate patients' deconditioning, AF symptoms and poor quality of life.[66]

We did not find significant increases in the overall severity of patient symptoms during the exercise weeks when compared to the Control week. The severity of palpitations, the most frequently reported symptom by patients with AF,[67] was higher during the control than HIIT week in females but not males. The reason for this result is unclear. Typically, a 20% greater proportion of females than males report palpitations.[67] A larger sample may have revealed worse severity of palpitations in females than males, yet our findings were not significant (sex effects on the severity of palpitations: $p=0.067$). Contrary to patients'

concerns regarding potential acute increases in AF symptoms with exercise training, exercise may mitigate some of these symptoms in the short-term. Confirming such findings in a larger sample would be reassuring for patients: combined with the evidence supporting the chronic (e.g., the effects of a 12-week exercise program) benefits of exercise training for the management of AF symptoms,[14,15] it may encourage clinicians to discuss and patients to engage in regular physical activity. Further, such analyses in more symptomatic patients are needed. Even though participants in the Acute-AF study reported at least two AF symptoms at baseline, the severity of symptoms was low during the study. Floor effects may have reduced our ability to detect changes in patient symptoms between conditions and sexes.

Mood and heart rhythm. Participants did not experience significant changes in their mood during the study weeks. This finding was considered positive, as it could have acted as a confounding factor for changes in their AF symptoms.[34] Since this sample included patients with non-permanent AF, we expected that not all participants would be in AF during the study conditions. In two males, none of the recorded ECGs showed AF. Monitoring patient AF symptoms and rhythm for a longer period (e.g., for additional weeks or using a 24-hour continuous heart rhythm monitor) may have enabled us to capture more AF episodes and symptoms. Interestingly, one female who showed AF some of the time during the study period noted that the mere participation in this trial disrupted their typical routine (e.g., early visits at the UOHI, parking) and they felt more AF episodes than they normally would. Stress related to the research trial may have affected their symptoms, as many females identify stress as the most frequent AF trigger.[68]

Acute responses to HIIT and MICT. The lack of evaluations in the AF population of acute physiological and psychosocial responses to exercise of different intensities may further contribute to patients feeling uninformed and hesitant about exercising.[6–8] In our previous cross-sectional survey (n=619, 34% female) in patients with AF, negative outcome

expectations (i.e., perceived harm from engaging in a behaviour) regarding physical activity were associated with lower self-reported physical activity levels.[69] Nearly one third of patients agreed with "If I tried to be physically active, my irregular heart rhythm would worsen", and nearly 40% agreed with "It is really not safe to be physically active with my AF if my HR becomes too fast."[69] Thus, informing patients about the typical acute responses to exercise may change their perceptions and enhance physical activity participation.

Overall, the acute responses to HIIT and MICT revealed increases in patient HR, perceived exertion, and blood pressure during exercise. The presence of AF may not substantially alter the physiological response to exercise; visual inspections of the graphs suggest that participant responses to exercise of several intensities are similar to findings in other CVD populations.[70–72] However, the accuracy of HR monitoring is limited. The percent HR_{peak} data should be interpreted with caution as, for instance, establishing a HR_{peak} during the baseline exercise test was difficult due to HR variability from AF, and due to using a 3-lead, instead of a standard 12-lead ECG. HR ranges are often used for exercise prescription in CVD populations,[73,74] yet alternative methods such as PPO are preferred for those living with a cardiac arrhythmia. Participants in the Acute-AF study showed excellent compliance with the exercise prescriptions, which were monitored using PPO; females and males with non-permanent AF were able to engage in weekly exercise that aligns with the World Health Organization physical activity guidelines.[50]

The perceived exertion and enjoyment of the sessions did not differ across exercise types or sexes. In patients with heart failure (n=134, 70±14 years old, 35% females), exercise enjoyment was positively associated with self-reported physical activity levels.[24] Our PACES scores are similar to those reported in patients with CVD attending cardiovascular rehabilitation (64±10 years old, 20% females; 102±22/126 points),[75] and suggest that 25-min HIIT and 50-min MICT may be appealing for patients with AF. The high compliance end

enjoyment reported by both sexes suggests HIIT and MICT as potential exercise options for these patients. Interestingly, HIIT but not MICT may acutely decrease anxiety levels. We did not conduct analyses on changes in affective valence given the numerous data points and small sample. This merits examination once a larger sample size has been reached, as identifying exercise prescriptions that elicit positive changes in affect during and following exercise may facilitate long-term physical activity participation.[76]

Adverse events during the study. Four non-serious adverse events were reported during the study period. One female had an unexpected event of moderate severity, they developed tachycardia at home one afternoon following a MICT session; this was confirmed by the KardiaMobile device showing "tachycardia", which prompted the patient to search this term on the web, causing anxiety and calling the paramedics. This adverse event shows that closer monitoring during the study period (e.g., use of daily ECGs and symptom diary) may cause patients to be more anxious and aware of symptoms. One female developed musculoskeletal shoulder pain following the HIIT week, which did not interfere with the remaining sessions as it subsided by the time the wash-out week ended. One male had a hypertensive crisis during the baseline appointment, which they associated with anxiety related to the research study – this prompted the participant to withdraw from the study. These two events may have been related to the study. Finally, another female had a fall at home leading to bruises. This may have interfered with the survey responses, as the event occurred at the beginning of the Control week.

In the general population, higher levels of physical literacy (i.e., competence, confidence and knowledge to be physically active) have been associated with higher physical activity levels.[77] With the Acute-AF study, we anticipated that improving our understanding of the short-term effects and acute responses to exercise in symptomatic patients with non-permanent AF, followed by disseminating the results with patients and clinicians, may

enhance physical activity participation and prescription. For instance, some patients with AF (N=20 females and 21 males, 64±10 years old) understand that their symptoms of dyspnea are partly due to their deconditioning ("being out of shape") and are keen to resume or start their exercise routine.[7]

Strengths and limitations

The present study has several strengths and limitations to consider. The daily assessment of heart rhythm, and the inclusion of physiological and psychosocial measures, as well as a wash-out week to minimize carry over effects, are considered strengths. Even though we did not meet our sample size of 20 participants (17 participants consented, 14 analyzed), the crossover design increases the power of our statistical analyses. Since the Acute-AF trial is ongoing, I will perform the analyses with a larger sample for manuscript publication. The current results should be interpreted with caution as, in some instances, we may not have reached statistical significance due to limited power. The lack of validation of the patient diary to report AF symptoms over 7 days is a limitation. However, a comprehensive list of symptoms typically reported by patients with AF were included in the diary. This list was based on other widely used (AFSS: University of Toronto AF severity scale) and validated (AFEQT: AF effect on quality-of-life) surveys in patients with AF, and on scientific and clinical expertise. Further, the KardiaMobile devices may not have captured all AF episodes during the study (e.g., no continuous monitoring). Since patients with paroxysmal AF were only considered eligible following an amendment on November 2022, few (18%) participants had paroxysmal AF. A better balance across the two non-permanent AF subtypes is anticipated with the continuation of the trial. The mean baseline $\dot{V}O_{2peak}$ was higher than seen in the general AF population, yet our values were similar to those reported in a previous exercise trial in patients with AF.[78] Selection bias may have attracted fitter and less

symptomatic patients given the exercise nature of the study. This limits the generalizability of our findings. Finally, only several questions of the Genesis-praxy survey were reported, and we were unable to compute a composite gender score given methodological limitations found *a posteriori* with this survey (e.g., the survey includes several modified scales for which scoring is not openly available for the public; only studies with a large sample size may be able to compute the gender score using principal component analysis).[41,42]

3.7. Conclusion

The preliminary results of the Acute-AF study provide novel data on sex differences in short-term changes in the severity of patient-reported AF symptoms with exercise, and a unique description of the acute physiological and psychosocial responses to exercise by sex in patients with symptomatic non-permanent AF. No differences in the overall symptom severity score, or the severity of most patient symptoms, were observed across the three study conditions (i.e., a week of HIIT, MICT and Control) or between females and males. Palpitation severity was lower during the HIIT than Control week in females, but not males. HR monitoring accuracy is compromised in patients with AF, as such, alternative methods to prescribe and monitor exercise intensity, such as PPO, may be warranted. Females and males reported similar enjoyment following HIIT and MICT, yet only HIIT may acutely improve anxiety levels. Confirming these findings in a larger sample will further improve our understanding of the short-term and acute responses to exercise in females and males with AF.

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3.9. Supplemental material

Appendix 3.1. – Consolidated Standards of Reporting Trials (CONSORT): Checklist of items that should be included in reports of randomized crossover trials

Section/topic	Item	Description
Title†	1a	Identification as a randomised crossover trial in the title.
Abstract†	1b	Specify a crossover desig..
Introduction:		
Background‡	2a	Scientific background and explanation of rationale.
Objectives‡	2b	Specific objectives or hypotheses.
Methods:		
Trial design†	3a	Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect.
Change from protocol‡	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.
Participants‡	4a	Eligibility criteria for participants.
Settings and location‡	4b	Settings and locations where the data were collected.
Interventions†	5	The interventions with sufficient details to allow replication, including how and when they were administered.
Outcomes‡	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed.
Changes to outcomes‡	6b	Any changes to trial outcomes after the trial commenced, with reasons.
Sample size†	7a	How sample size was determined, accounting for within participant variability.
Interim analyses and stopping guidelines‡	7b	When applicable, explanation of any interim analyses and stopping guidelines.
Randomisation:		
Sequence generation‡	8a	Method used to generate the random allocation sequence.
Sequence generation‡	8b	Type of randomisation; details of any restriction (such as blocking and block size).

Allocation concealment mechanism‡	9	Mechanism used to implement the random allocation sequence§ (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.
Implementation†	10	Who generated the random allocation sequence,§ who enrolled participants, and who assigned participants to the sequence of interventions.
Blinding‡	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.
Similarity of interventions‡	11b	If relevant, description of the similarity of interventions.
Statistical methods†	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison).
Additional analyses‡	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow (a diagram is strongly recommended)†	13a	The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period.
Losses and exclusions†	13b	No of participants excluded at each stage, with reasons, separately for each sequence and period.
Recruitment‡	14a	Dates defining the periods of recruitment and follow-up.
Trial end‡	14b	Why the trial ended or was stopped.
Baseline data†	15	A table showing baseline demographic and clinical characteristics by sequence and period.
Numbers analysed†	16	Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups.
Outcomes and estimation†	17a	For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons.¶ In addition, results for each intervention in each period are recommended.
Binary outcomes‡	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended.
Ancillary analyses‡	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.

Harms†	19	Describe all important harms or untended effects in a way that accounts for the design.
Discussion		
Limitations†	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects.
Generalisability‡	21	Generalisability (external validity, applicability) of the trial findings.
Interpretation‡	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.
Other information:		
Registration‡	23	Registration number and name of trial registry.
Protocol‡	24	Where the full trial protocol can be accessed, if available.
Funding‡	25	Sources of funding and other support (such as supply of drugs), role of funders.

*Note: page numbers are optional depending on journal requirements.

†Modified original CONSORT item.

‡Unmodified CONSORT item.

§Random sequence here refers to a list of random orders, typically generated through a computer program. This should not be confused with the sequence of interventions in a randomised crossover trial, for example receiving intervention A before B for an individual trial participant.

¶A within participant comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not

independent.

Appendix 3.2. Criteria to consider patients in the Acute-AF study symptomatic

Patients were considered symptomatic if they reported at least two AF-related symptoms in the past 4 weeks,[2,13] including: (1) heart fluttering/ racing/ skipping beat/ palpitations, (2) difficulty breathing/ shortness of breath at rest, (3) difficulty breathing/ shortness of breath during physical activity, (4) exercise intolerance or fatigue during mild physical activity, (5) weakness/ fatigue at rest, (6) light-headedness/ dizziness/ presyncope or syncope, (7) chest pain or pressure, (8) anxiety/ agitation during AF, (9) AF-related difficulty sleeping, (10) nausea, and (11) sweating.

Appendix 3.3. Patient diary to report atrial fibrillation symptoms over 7 days

PATIENT DIARY FOR SYMPTOMS

1. Please indicate on a scale of 0-10 how severe the symptoms were of this episode of irregular heart rhythm. 0 being no symptoms, 1 being not severe at all and 10 being extremely severe. Please indicate the length of time (in minutes) the symptoms persisted.
2. In the far right column, please indicate on a scale of 0-10 how severe overall were the symptoms. 0 being no symptoms, 1 being not severe at all and 10 being extremely severe (Do not take into account the length of the episodes).

	Heart fluttering/racing/ skipping beat/ palpitating	Difficulty breathing/shortness of breath	Fatigue/weakness	Dizziness	Nausea	Sweating	Difficulty sleeping	Anxiety/agitation	Other (explain)	Overall symptoms
Day 1	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 2	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 3	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 4	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 5	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 6	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)
Day 7	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min)	___ (0-10) ___ (min) _____	___ (0-10)

Day 1	Notes (if any):
Day 2	Notes (if any):
Day 3	Notes (if any):
Day 4	Notes (if any):
Day 5	Notes (if any):
Day 6	Notes (if any):
Day 7	Notes (if any):

Appendix 3.4. Duration (minutes) of patient atrial fibrillation symptoms by sex and condition week.

		HIIT	MICT	Control
Palpitations duration	Females	46.5 ± 34.6	94.5 ± 112.4	38.9 ± 47.9
	Males	1.9 ± 5.0	180.0 ± 509.1	3.1 ± 6.7
Dyspnea duration	Females	2.5 ± 5.0	60.0 ± 120.0	0.4 ± 0.8
	Males	5.4 ± 6.8	4.9 ± 7.0	4.2 ± 7.8
Fatigue duration	Females	40.0 ± 69.3	73.2 ± 113.5	3.3 ± 5.8
	Males	7.2 ± 11.1	56.2 ± 110.0	8.2 ± 12.8
Dizziness duration	Females	4.6 ± 9.3	0.4 ± 0.7	0.3 ± 0.5
	Males	0.1 ± 0.3	4.3 ± 7.9	0.0 ± 0.0
Difficulty sleeping duration	Females	6.7 ± 11.6	9.3 ± 13.5	30.0 ± 60.0
	Males	14.4 ± 20.2	29.3 ± 39.8	30.4 ± 49.8
Anxiety or agitation duration	Females	30 ± 42.4	51.7 ± 70.8	15.0 ± 30.8
	Males	7.1 ± 11.5	5.7 ± 11.9	3.0 ± 6.7

Data presented as means ± standard deviations. HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training.

CHAPTER 4 - A cross-sectional sex comparison of the physical and mental health profile of patients with persistent and permanent atrial fibrillation

PREAMBLE TO STUDY 2

Chapter 4 focuses on sex-based analyses of the physical and mental health profile, as well as physical activity levels, of patients with persistent and permanent atrial fibrillation (AF). Several clinical sex differences have been noted in patients with AF, such as females being older and having a heightened risk for stroke and mortality than males. Yet, sex differences in many important health measures and behaviours remain unclear. By comparing modifiable health characteristics and behaviours between sexes, we can identify which factors should be preferentially targeted by sex-specific treatments for patients with AF. Further, by examining associations between the measured health characteristics in each sex, we may provide the foundation for future large scale randomized controlled trials to examine mechanisms underpinning potential sex differences in patients with AF. Study 2 includes baseline data of the Opportunity and Exercise-AF trials.

4.1. Abstract

Background: There is a scarcity of sex-based health outcomes analyses in patients with atrial fibrillation (AF). **Aim:** To cross-sectionally compare physical and mental health characteristics, and moderate- to vigorous-intensity physical activity (MVPA) levels, between females (F) and males (M) with persistent and permanent AF. **Methods:** The primary outcome of this observational study, peak aerobic power ($\dot{V}O_{2peak}$), was measured with a cardiopulmonary exercise test. AF symptoms, AF-specific quality of life (QoL) and general QoL were reported by patients. Additional measures included functional capacity (6-minute walk test), resting heart rate and blood pressure, body mass index (BMI), waist circumference, body composition, anxiety and depression (Hospital Anxiety and Depression Scale), and MVPA levels measured with an accelerometer. Independent t-tests and Mann-Whitney U tests were used for sex comparisons for continuous variables. Chi-square analyses were used for categorical variables. **Results:** A total of 39 females and 39 males (F: 71±7, M: 70±7 years old) were included. Females had a lower $\dot{V}O_{2peak}$ than males (F: 14.6±3.8 vs. M: 19.1±5.0 mL O_2/kg/min, $p<0.001$). No sex difference was observed in $\dot{V}O_{2peak}$ after adjusting for fat-free mass (FFM) (24.4±6.1 vs. 26.2±6.7 mL O_2/kg of FFM/min, $p=0.228$). More females than males reported palpitations (64% vs. 31%, $p=0.003$). Females reported a 4.5-point higher general health score ($p=0.028$), and had a higher resting heart rate (76±14 vs. 69±14 bpm, $p=0.029$) and body fat (36±7% vs. 27±7%, $p<0.001$) than males. No sex differences were observed in AF-specific and general QoL summary scores, functional capacity, blood pressure, BMI, anxiety, depression, or MVPA levels. **Conclusions:** $\dot{V}O_{2peak}$ was 27% lower in females than males with AF; adjusting for FFM narrowed the sex gap to 7%. More females reported palpitations. Several modifiable risk factors (e.g., only F: 34%, M: 41% met ≥150 min/week of MVPA) were prevalent, highlighting a need for lifestyle strategies; these may particularly mitigate females' symptoms and poor physical health.

4.2. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, afflicting 17.8 million females and 19.8 million males globally (F: 47.3%, M: 52.7%), and more than 450,000 people in Canada.[1] AF often co-exists with several cardiovascular disease (CVD) risk factors, and confers a high risk of morbidity and mortality.[2] There are sex-unique manifestations of AF. Females with AF have a 20 to 30% greater risk of stroke[3,4] and heart failure,[5] and are at an increased risk for hospitalization[5] and mortality (male to female ratio: 0.79)[6] than males. Females experience more side effects from heart rhythm and rate control medications,[7] and have worse procedural outcomes including greater rates of complications[8–11] and AF recurrence[5,10] during and following a catheter ablation. Females, thus, are impacted to a greater extent by AF, as has been shown in those with CVD.[12]

Such emerging sex differences in AF warrant additional sex-specific analyses to improve our understanding of the clinical presentation of patients with AF. In turn, this may help practitioners choose individualized therapeutic approaches that meet the unique needs of females and males. Despite ongoing calls for sex-based analyses, less than 30% of AF randomized controlled trials (RCTs) published in top-tier journals (based on Clarivate Analytics impact factor 2020) between 2011 and 2021 reported outcomes by sex, and females were largely underrepresented.[13] Publications in the field of exercise medicine - an important health behaviour for the management of patients with AF - also show a concerning female underrepresentation (only 10 to 35% of participants were female), which has not improved over time.[14–17] As a result of such inequalities, the current clinical guidelines for the management of patients with AF may not be applicable to both sexes.[18]

Many sex and gender knowledge gaps remain in the AF literature. Some clinical sex differences are better established (e.g., females often report greater symptom frequency and severity[19–21] and poorer quality of life [QoL][22]), but there are additional physical and mental

health characteristics (e.g., peak aerobic power [$\dot{V}O_{2peak}$], functional capacity, anxiety, depression), and health behaviours (e.g., moderate- to vigorous-intensity physical activity [MVPA] levels), which have been shown to influence the symptomatology and pathogenesis of AF[23] and risk for adverse events.[24] Yet, they remain understudied with regards to sex.

Maintaining healthy lifestyle behaviours (e.g., participating in exercise training) is an increasingly recognized care approach for improving patient AF symptoms and QoL, managing patient CVD modifiable risk factors (e.g., reduce blood pressure, body mass, anxiety and depression),[25,26] and lowering the risk for major adverse cardiovascular events.[24] $\dot{V}O_{2peak}$ is a gold-standard health measure for patients with AF due to its prognostic value.[27] $\dot{V}O_{2peak}$ is 15 to 20% lower in patients with AF than those in sinus rhythm.[28,29] An elevated left ventricular filling pressure and diminished chronotropic response have been shown to contribute to the reduced $\dot{V}O_{2peak}$ in those living with AF.[30] In a recent cohort study (n=304 with AF, 27% females), patients with a high fitness level at cardiovascular rehabilitation (CR) entry had a 0.41 hazard ratio (95% confidence interval [CI] 0.24 to 0.70, $p<0.001$) for CVD hospitalization or all-cause mortality during the 5-year follow-up.[31] Fitness as estimated by metabolic equivalents (METs) was the strongest predictor of the above mentioned endpoints.[31]

In healthy and CVD populations, females often have a 20 to 30% lower absolute $\dot{V}O_{2peak}$ (L O_2/min) than males.[32] This disparity is explained by sex differences in body anthropometry and composition; males generally have a greater body size and mass, lower body fat and higher muscle mass than females.[32] To facilitate more appropriate comparisons between sexes, $\dot{V}O_{2peak}$ is better expressed in relative forms adjusted for body mass (mL O_2/kg/min) or fat-free mass (FFM) (mL O_2/kg of FFM/min). The latter reduces the magnitude of the $\dot{V}O_{2peak}$ sex difference to approximately 12% to 15%.[32] The scarce sex-specific exercise physiology data in patients with AF[33] suggest a markedly lower $\dot{V}O_{2peak}$ in females

than males (N=210, 28% females; F: 18.1±6.8 vs. M: 25.4±7.5 mL O_2/kg/min).[34] Differences in health behaviours such as lower MVPA levels in females may contribute to their lower $\dot{V}O_{2peak}$.[32] Yet, few $\dot{V}O_{2peak}$ and physical activity data are available by sex in AF.[35] The latter have been mostly self-reported, a method that introduces social desirability bias.[36] For instance, in our Champlain-AF cohort study (N=621 with AF, 33% females), females reported similar MVPA as males (median [95% CI]; F: 60 [0 to 142], M: 120 [90 to 155] weekly minutes, p=0.132).[37]

Females' greater symptomatology may be attributed to their poorer physical and mental health profile, and unhealthier lifestyle behaviours than males. For instance, lower $\dot{V}O_{2peak}$[34] and MVPA levels,[35] and higher rates of obesity and high-risk waist circumference[35,38] may lead to greater symptoms of dyspnea,[21] palpitations,[21,22,35,39] fatigue[21,22,35] and fear/anxiety[20] during activities of daily living in females. Exploring such associations in each sex may tease out potential mechanisms of the pathophysiology and symptomatology in patients with AF. By comparing the health profile between sexes, we may inform which health characteristics and behaviours should be preferentially targeted by therapeutic interventions in females and males.

4.3. Objectives and hypotheses

The primary purpose of this study was to compare $\dot{V}O_{2peak}$ between females and males with persistent and permanent AF. It was hypothesized that females with AF would demonstrate a lower $\dot{V}O_{2peak}$ than males, even after adjusting for body mass and FFM. The secondary aim was to compare additional physical and mental health characteristics (i.e., patient AF symptoms, QoL, functional capacity, hemodynamic and anthropometric measures, anxiety and depression), and health behaviours (i.e., device measured MVPA levels), between sexes. It was hypothesized that females would report more frequent and severe AF symptoms, and

poorer QoL; have worse functional capacity; have higher resting HR and BP, BMI and body fat percentage; have lower waist circumference and FFM; report greater symptoms of anxiety and depression; and, engage in fewer weekly minutes of MVPA than males with AF.

4.4. Methods

Study design and setting

This was a cross-sectional observational study. Baseline data from two RCTs, the Opportunity (ClinicalTrials.gov #NCT02602457) and Exercise-AF (ClinicalTrials.gov #NCT03397602) trials, were used. The studies were conducted at the University of Ottawa Heart Institute (UOHI), a tertiary care cardiovascular centre located in Ottawa, Ontario, Canada. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines were followed (see Appendix 4.1.).[40] Based on the Sex and Gender Equity in Research (SAGER) guidelines,[41] an equal number of females and males were included to facilitate sex-based analyses.[41] Consecutively enrolled females and males were included until the sample size for each sex was achieved. Approval was obtained from the Ottawa Health Science Network Research Ethics Board (protocol #: 20150427; protocol #: 20180342).

Participants

Participants were recruited between November 2015 and December 2022 (this date limit was selected given the student's timeline; recruitment for the Exercise-AF trial is ongoing). Recruitment sources included referrals from UOHI physicians, or through the distribution of posters or newsletters to community and medical centres in the National Capital Region of Canada. All participants provided written, informed consent. Eligible patients included those who: (1) had persistent or permanent AF as confirmed by a physician; (2) were rate-

controlled with a resting heart rate (HR) ≤110 bpm; (3) were able to perform an exercise test to exhaustion (since this RCT involved exercise); (4) were ≥40 years of age; and, (5) were able to read and understand English or French. Patients were excluded if they were: (1) participating in exercise training >2 days per week; or, (2) diagnosed with unstable angina, uncontrolled diabetes, severe mitral or aortic stenosis, or hypertrophic obstructive cardiomyopathy.

Health measures

All health measures were collected during the baseline visit at the UOHI.

Sex and sociodemographic/gender-related data

Sex was retrieved from the UOHI's electronic medical records system and was based on the legal sex assigned to each patient at birth.[42] Socio-demographic and gender-related data including personal income, level of education, employment status and ethnicity were self-reported by patients at baseline with a questionnaire.

Primary outcome

Peak aerobic power ($\dot{V}O_{2peak}$)

$\dot{V}O_{2peak}$ was measured using an incremental (2-minute warm-up at 40 W, 20 W-increment per minute, 3-minute cool-down at 40 W) cardiopulmonary exercise test (CPET) to volitional exhaustion on an electrically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany; or, Cosmed, United States). The test was supervised by certified study staff (e.g., Clinical Exercise Physiologists) or cardiac stress technologists from the Department of Cardiac Imaging at the UOHI. Ratings of perceived exertion (RPE) were reported every minute using the 6-20 Borg scale[43] to determine participants' level of effort. Gas exchange

was continuously monitored during the test using a metabolic cart that collects breath-by-breath data through open-circuit indirect calorimetry (Oxycon Mobile Carefusion; or, Cosmed, United States). In the general population, $\dot{V}O_2$ values from the Oxycon Mobile and Cosmed devices have been shown to agree with those measured using the Douglas bag method over a wide range of exercise intensities (n=60 adults, 3% females, 30±5 years old; n=32 males, 23±4 years old[44]).[45] The highest 20-second average of oxygen uptake in mL O_2/kg/min represented $\dot{V}O_{2peak}$. To account for differences in body composition between sexes, $\dot{V}O_{2peak}$ was further adjusted for FFM.[46] The proportion of females and males within different cardiorespiratory fitness categories were calculated based on the American College of Sports Medicine (ACSM) classifications for the general population.[47]

Secondary outcomes

AF symptoms

Patient AF symptoms and their impact on patient's functionality was measured using the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale (CCS-SAF),[48] a simple 3-step scale using closed questions (yes/no). The CCS-SAF comprises: (1-S) identification of AF-related symptoms (i.e., palpitations, dyspnea, dizziness, presyncope or syncope, chest pain, weakness or fatigue, other); (2-A) determination of the correlation between patient symptoms and AF rhythm (i.e., *is AF, when present, associated with the above-listed symptoms?*); and, (3-F) self-assessment of the impact of these symptoms on patient's daily functionality. Few studies have validated the CCS-SAF in patients with AF (n=484, 62% paroxysmal AF, 38% persistent/permanent, 67% males, 62±13 years old) against the University of Toronto Atrial Fibrillation Severity Scale (AFSS)[49] and the Medical Outcomes Study Short-Form (SF-36)[50] questionnaires.

AF-specific QoL

AF-specific QoL was measured using the AFSS questionnaire, a widely used self-report survey assessing subjective and objective ratings of AF burden.[49] The AFSS questionnaire comprises three sections. *Part A*: overall well-being is rated on a 1 (worst possible life) to 10 (best possible life) visual analogue scale, and the AF burden score (range: 3 to 30 points) is calculated from the frequency, severity, and duration of symptomatic AF episodes. *Part B*: four items assess healthcare utilization in the previous year. *Part C*: seven items assess symptom severity over the previous 4 weeks, each are scored from 0 ("very little") to 5 ("a great deal"), leading to a symptom severity score between 0 to 35 points. For the overall well-being, higher scores denote better perceived health. For the other sections of the AFSS, higher scores indicate greater AF burden.

General QoL

General QoL was measured using the SF-36 v.1,[50] a 36-item self-report survey assessing general health over the previous 4 weeks. The SF-36 yields an 8-scale profile of functional health and well-being scores (i.e., physical functioning; role limitations due to physical problems; bodily pain; general health perceptions; energy/vitality; social functioning; role limitations due to emotional problems; and mental health) as well as psychometrically-based Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Higher scores denote better perceived health.[33,51] The SF-36 is widely validated in CVD populations[52,53] and has been used in patients with AF.[33,51] In patients with a previous myocardial infarction (n=421, 66% males, 66±10 years old), items in the same domain of the SF-36 have shown good internal consistency (Cronbach's $\alpha \geq 0.80$) and the SF-36 subscales have moderate-to-high (r=0.52 to 0.73) correlation with those of the Nottingham Health Profile survey, a QoL survey intended for primary care.[52]

Functional capacity

Patient functional capacity was assessed with the six-minute walk test (6MWT). Participants were instructed to walk on an indoor track as far as possible for 6 minutes, and the distance achieved was measured in metres. Walking a longer distance denotes better functional capacity. Walking a distance shorter than 450 metres has been associated with increased symptom burden,[54] thus, this cut-off was used to define patients with a low functional capacity. The 6MWT is a valid and practical field test often used in CR settings.[55,56]

Hemodynamic measures

Resting HR and blood pressure were collected in a seated position with an automated HR and blood pressure sphygmomanometer monitor (Welch Allyn, Canada). Patients remained seated for 5 minutes prior to the measurement and were asked to keep their feet flat on the ground without crossing the legs. Three measurements were taken with at least 2 minutes in between, and the average was calculated and used for analyses.[47]

Anthropometric measures

Body mass was measured using a digital scale (Health o meter® Heavy Duty Remote Digital Scale 752KL or Omron HBF-514C) to the nearest 0.1 kg and height was measured using a SECA 206 height measuring system to the nearest 0.1 cm. BMI was calculated based on the body mass and height (kg/m^2). Waist circumference was measured at the midpoint between the lower costal margin and iliac crest while patients stood with arms at the sides, feet shoulder width apart and abdomen relaxed after a full exhalation using a SECA 201 tape measure to the nearest 0.1 cm.[47] Triplicate measurements were taken, and the average was used for analyses. The proportions of participants across BMI (underweight: <18.5 kg/m^2,

normal: 18.5 to 24.9 kg/m^2; overweight: 25.0 to 29.9 kg/m^2, obesity ≥30 kg/m^2) and high-risk waist circumference (females: ≥88 cm; males: ≥102 cm) categories were calculated.[47]

Body composition was measured using a digital scale (Tanita FitScan UM-041F, Omron HBF-514C, Inc, Arlington Heights, IL), which estimates percent body fat by hand-to-foot bioelectrical impedance analyses to the nearest 0.1%. Body mass and percent body fat were then used to calculate FFM (body mass - [body mass × % body fat / 100]). Participants were given pre-testing guidelines for bioelectrical impedance testing to minimize variability due to external factors (e.g., avoid electrolyte imbalance),[57,58] including: (i) no eating or drinking for 4 h; (ii) no MVPA for 12 h; (iii) no alcohol consumption for 48 h; (iv) to void their bladder within 30 min; and, (v) to refrain from consuming caffeine and non-prescribed diuretic use for 12 h. Participants were instructed to step barefoot on the scale, stand upright, hold the display unit with both hands and extend the arms parallel to the floor for 5-10 seconds. These scales have shown good validity in both sexes compared to other low-cost tools for bioelectrical impedance analysis.[58,59] In healthy older adults (n=50, 66% female, 56 to 94 years old) the Tanita hand-to-foot and the foot-to-foot method have shown high correlation ($r=0.84$, $p<0.001$) for percent body fat.[58] In healthy young adults, low-cost scales have shown high correlation with air displacement plethysmography, a widely validated method for body composition assessment ($r=0.97$ to 0.98).[59]

Anxiety and depression symptoms

Symptoms of anxiety and depression over the previous week were measured using the 14-item Hospital Anxiety and Depression Scale (HADS).[60] Each item is rated on a 4-point scale (0-3 points). It yields separate anxiety and depression scores (7 items each); the subscale scores range from 0-21 points and >7 points are considered elevated. The HADS has good psychometric properties in cardiac patients (n=591, 26% females, 63±10 years old), with high

internal consistency for anxiety (Cronbach's α=0.86) and depression (Cronbach's α=0.82),[61] and strong correlation with other widely used scales such as the Patient Health Questionnaire-9 (r=0.72).[62] The proportion of patients with elevated anxiety or depression was calculated. The HADS was only administered in the Opportunity trial following an ethics amendment after the trial had begun.

Physical activity levels

Physical activity was measured using an accelerometer (ActiGraph GT3X, Pensacola, Florida) worn over the right hip on a waist belt during waking hours for seven days, excluding periods when participants engaged in water-related activities (i.e., bathing, swimming). The ActiGraph GT3X is a small wearable accelerometer frequently used in research for the assessment of MVPA levels in free-living conditions. It has shown good validity to measure physical activity in healthy and older adults.[63–66] In 50 (50% female, 24±3 years old) and 42 (45% female, 22±3 years old) adults, activity counts as measured by uniaxial[66] and triaxial[64] accelerometers highly correlated with steady-state oxygen consumption measured with a metabolic cart (r=0.88 and 0.81, respectively). In older adults, some studies using ActiGraph accelerometer counts (n=62, 79% females, 75±7 years old, r=0.5 to 0.6) and other triaxial accelerometers (n=29, 60 to 80 years old, r=0.85) suggest a moderate-to-strong correlation with measured physical activity energy expenditure measured using the Douglas bag method.[65,67]

The physical activity analyses were conducted using the ActiLife software (v.6.13.4, ActiGraph, LLC). The tri-axial GT3X captures movement about the vertical (y), horizontal (x) and perpendicular (z) axes, creating a composite vector magnitude of the three axes which was used for the analysis (VM3, $\sqrt{[x^2+y^2+z^2]}$). The ActiLife software converts the raw acceleration data into activity counts and steps. Details on how to process accelerometer data

have been described by others.[68,69] In summary, non-wear time was defined as a minimum of 60 minutes of consecutive zero counts and was excluded from the analyses. A valid day of physical activity data was defined as ≥10 hours of wear-time and only patients with ≥4 valid days were retained in the analyses. Vector magnitude Sasaki cut-points were chosen to define light (150-2,689 counts-per minute [cpm]), moderate (2,690-6,166 cpm) and vigorous (≥6,167 cpm) physical activity.[69,70] Weekly minutes of physical activity at each intensity were calculated by multiplying the daily average (min/day) by seven. To minimize reactivity, the first day was removed and the subsequent days were used for the average. These cut-points were developed in a healthy, young population (n=36, sex distribution unknown) and deserve further validation, yet they have been used to assess physical activity levels in patients with AF[71] and CVD.[68,72,73] Further, MVPA levels determined using Sasaki cut-points have been shown to strongly correlate (r=0.91) with Mark cut-points; the latter were developed in patients with CVD, but they may over-estimate the proportion of patients meeting MVPA guidelines.[69] Using the Sasaki cut-points, the proportion of patients meeting ≥200 minutes per week of moderate-intensity exercise training, as recommended by the CCS AF management guidelines,[18] as well as ≥150 weekly minutes of MVPA, as recommended by the Canadian 24-hour movement guidelines for adults,[74] were calculated.

Sample size

G*Power Version 3.1.9.4 (Kiel University, Germany) was used to calculate the sample size to test the primary hypothesis of sex comparisons of $\dot{V}O_{2peak}$. Mean differences between sexes and standard deviations of patients with AF entering CR (N=59 females and 159 males) were used to calculate an effect size.[34] Wagner *et al*. reported a large effect size (0.9) for sex differences in $\dot{V}O_{2peak}$ at baseline, yet they did not account for sex differences in FFM.[34] Since the FFM adjustment in the study was expected to reduce the difference in $\dot{V}O_{2peak}$

between sexes, an effect size of 0.7 was considered appropriate. Using a two-sided 0.05 significance level, with 80% power (1-β), a total sample size of 68 (34 females and 34 males) was required to examine differences in $\dot{V}O_{2peak}$ (primary outcome) between sexes using Independent t-tests (see Appendix 4.2. for calculations). To maximize the power for our analyses, the highest equal number of females and males available was used.[41]

Statistical analyses

Statistical analyses were conducted using SPSS for Windows (version 29; IBMCorp, Armonk, New York, United States). All variables were tested for normality using Shapiro-Wilk tests. Descriptive statistics were used to summarize the sample characteristics by sex. Continuous variables are presented as means ± standard deviations. Categorical variables are presented as frequencies and percentages. Independent t-tests and Mann-Whitney U tests were used to compare the means of normally and non-normally distributed continuous variables, respectively, between females and males with AF. Chi-square analyses were used to compare categorical data between sexes. Pearson's correlation coefficients were used to determine the strength and direction of associations between $\dot{V}O_{2peak}$ or MVPA levels and other physical and mental health characteristics; these were performed in each sex separately. Significance was set at $p<0.05$ (two-sided).

4.5. Results

A total of 39 females and 39 males were included in the study. Participant sociodemographic and gender-related characteristics, CVD risk factors, previous medical conditions and prescribed medications are compared by sex in Table 4.1. The mean age in females and males was 71±7 and 70±7 years old, respectively, with an equal distribution of AF subtypes across sexes. No sex differences in sociodemographic and gender-related factors were observed;

participants were predominantly White, retired, with a college or university degree and earning at least $50K a year. Several CVD risk factors were prevalent among both sexes, with hypertension being the most prevalent (59% of participants). Most had a high-risk waist circumference and were categorized as overweight or obese. Anticoagulants and β-blockers were the most frequently prescribed medications in both sexes. A greater proportion of males were prescribed statins (F: 23% vs. M: 49%, p=0.018), and 10% of females were taking hormone replacement medications.

Table 4.1. Participant characteristics by sex.

	Females n=39	Males n=39	All N=78	P between sexes
Sociodemographic and gender-related data, n (%)				
Age (years), mean ± SD	71 ± 7	70 ± 7	70 ± 7	0.459
Atrial fibrillation subtype				1.000
Persistent	18 (46.2)	18 (46.2)	36 (46.2)	
Permanent	21 (53.8)	21 (53.8)	42 (53.8)	
Ethnicity: White	29 (90.6)	34 (89.5)	63 (81)	0.514
Work status: Retired	25 (78.1)	28 (73.7)	53 (67.9)	0.879
Education: College or university	25 (78.2)	27 (71.1)	52 (66.7)	0.109
Income: Earning 50K+ per year	15 (55.5)	26 (70.2)	41 (64.1)	0.272
Cardiovascular disease risk factors and previous medical conditions, n (%)				
Hypertension	21 (53.8)	25 (64.1)	46 (59.0)	0.357
High-risk waist circumference	19 (55.9)	21 (56.8)	40 (56.3)	0.941
Elevated body mass index				0.611
Overweight	10 (25.6)	14 (35.9)	23 (29.9)	
Obesity	18 (46.2)	16 (41.0)	34 (44.2)	
Dyslipidemia	7 (17.9)	13 (33.3)	20 (25.6)	0.120
Coronary artery disease	2 (5.1)	7 (17.9)	9 (11.5)	0.076
Diabetes	4 (10.3)	7 (17.9)	11 (14.1)	0.329
Obstructive sleep apnea	4 (10.3)	5 (12.8)	9 (11.5)	0.723
Heart failure	3 (7.7)	4 (10.3)	7 (9.0)	0.692
Transient ischaemic attack or stroke	5 (12.8)	2 (5.1)	7 (9.0)	0.235
Chronic obstructive pulmonary disease	1 (2.6)	2 (5.1)	3 (3.8)	0.556
Myocardial infarction	1 (2.6)	2 (5.1)	3 (3.8)	0.556
Valvular disease/ replacement	2 (5.1)	0 (0)	2 (2.6)	0.152
Smoker	0 (0)	2 (5.1)	2 (2.6)	0.152
Peripheral vascular disease	1 (2.6)	1 (2.6)	2 (2.6)	1.000
Ischemic cardiomyopathy	1 (2.6)	1 (2.6)	2 (2.6)	1.000
Medications, n (%)				
Anti-coagulant	36 (92.3)	34 (87.2)	70 (89.7)	0.455
β-blocker	24 (61.5)	29 (74.4)	53 (67.9)	0.225
Statin	9 (23.1)	19 (48.7)	28 (35.9)	**0.018**
Calcium channel blocker	13 (33.5)	11 (28.2)	24 (30.8)	0.624
Angiotensin II receptor blocker	11 (28.2)	9 (23.1)	20 (25.6)	0.604
Diuretic	10 (25.6)	9 (23.1)	19 (24.4)	0.792
ACE-inhibitor	4 (10.3)	12 (30.8)	16 (20.5)	0.025
Thyroid hormone	11 (28.2)	5 (12.8)	16 (20.5)	0.092
Digoxin	7 (17.9)	3 (7.7)	10 (12.8)	0.176
Anti-platelet	3 (7.7)	6 (15.4)	9 (11.5)	0.288
Oral hypoglycemic	2 (5.1)	6 (15.4)	8 (10.3)	0.135
Nitrate	1 (2.6)	5 (12.8)	6 (7.7)	0.089
Anti-depressant	1 (2.6)	4 (10.3)	5 (6.4)	0.165
Anti-arrhythmic	2 (5.1)	2 (5.1)	4 (5.1)	1.000
Hormone replacement therapy	4 (10.3)	0 (0)	4 (5.1)	**0.040**
Insulin	1 (2.6)	0 (0)	1 (1.3)	0.314

Data presented as n (percentage). P<0.05: significance. ACE: Angiotensin-converting enzyme.

Peak aerobic power. Females presented with a significantly lower $\dot{V}O_{2peak}$ than males (F: 14.6±3.8 vs. M: 19.1±5.0 mL O_2/kg/min, p<0.001; see Table 4.2.). Absolute $\dot{V}O_{2peak}$ was also significantly lower in females (F: 1.14±0.37 vs. M: 1.74±0.47 L O_2/min, p<0.001). No sex difference was observed after adjusting for FFM. The peak power output (F: 108±35 vs. M: 153±39 Watts, p<0.001) and RPE (F: 16±3 vs. M: 18±3 points, p=0.028) reached during the CPET were lower in females. The $\dot{V}O_{2peak}$ of 28 (72%) females and 30 (79%) males would be considered *very poor* as per ACSM's classification for the general population (F: <15.6, M: <21.2 mL O_2/kg/min for the 60-69 years old category).

Patient AF symptoms and QoL. Most self-reported AF symptoms as measured by the CCS-SAF did not differ between sexes (see Table 4.2.). Yet, a greater proportion of females than males reported palpitations (F: 64% vs. 31%, $\chi 2(1)=8.690$, p=0.003, Cramer's V=0.334). Most patients experienced fatigue (F: 59% vs. M: 67%, $\chi 2(1)=0.494$, p=0.482) and shortness of breath (F: 56% vs. M: 54%, $\chi 2(1)=0.052$, p=0.820). While no sex differences were noted in any of the AFSS measures (see Table 4.2.), most patients associated their symptoms with AF (F: 78% vs. M: 70%, $\chi 2(1)=0.534$, p=0.465), and felt that AF limited their functionality (F: 67% vs. M: 63%, $\chi 2(1)=0.100$, p=0.752). The total AF burden score, which considers the frequency, duration and severity of AF episodes reported by patients, was 21.4±5.1 points in females and 21.8±2.8 points in males. Among the SF-36 subscales, females reported significantly higher general health scores than males (46±9 vs. 41±8 points, p=0.028) (see Table 4.2.). Similar PCS and MCS scores were reported across sexes.

Functional capacity. The distance walked in the 6MWT did not differ significantly between sexes (see Table 4.2.). A total of 14 (37%) females and 11 males (28%) were deemed to have a low functional capacity, as they walked less than 450 metres (p=0.418).

Table 4.2. Sex comparison of physical and mental health measures, and physical activity levels, in patients with persistent and permanent atrial fibrillation.

	Females n=39	Males n=39	All N=78	P between sexes
Peak aerobic power				
$\dot{V}O_{2peak}$ (mL O_2/kg/min)	14.6 ± 3.8	19.1 ± 5	16.8 ± 5	**<0.001**
$\dot{V}O_{2peak}$ (mL O_2/kg of FFM/min)	24.4 ± 6.1	26.2 ± 6.7	25.4 ± 6.4	0.228
Peak power output (Watts)	108 ± 35	153 ± 39	130 ± 43	**<0.001**
AF symptoms (CCS-SAF), n (%)				
Fatigue	23 (59.0)	26 (66.7)	49 (62.8)	0.482
Dyspnea	22 (56.4)	21 (53.8)	43 (55.1)	0.820
Palpitations	25 (64.1)	12 (30.8)	37 (47.4)	**0.003**
Dizziness	14 (35.9)	13 (33.3)	27 (34.6)	0.812
Angina	5 (12.8)	1 (2.6)	6 (7.7)	0.089
AF-specific quality of life (AFSS), points				
Global wellbeing (1-10)	7.4 ± 1.9	7.4 ± 1.7	7.4 ± 1.8	0.928
Frequency of AF (1-10)	2.1 ± 1.7	1.4 ± 1.1	1.7 ± 1.4	0.053
Duration of AF (1-10)	2.5 ± 2.5	1.7 ± 2	2.1 ± 2.3	0.083
Severity of AF (1-10)	4.1 ± 2.7	3.3 ± 2	3.8 ± 2.4	0.209
Visits to emergency department	0.6 ± 1.3	0.3 ± 0.7	0.5 ± 1.1	0.403
Hospitalizations	0.1 ± 0.4	0.2 ± 0.7	0.2 ± 0.5	0.408
Specialist visits	1.4 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	0.581
Total burden (0-30)	21.4 ± 5.1	21.8 ± 2.8	21.6 ± 4.1	0.894
Symptom score (0-35)	9.5 ± 6.4	7.9 ± 5.1	8.7 ± 5.8	0.225
General quality of life (SF-36), points (0-100)				
Physical functioning	42.7 ± 9.7	41.3 ± 9.5	42 ± 9.6	0.437
RL – physical problems	41.7 ± 11.7	42.1 ± 12.0	41.9 ± 11.8	0.879
Bodily pain	36.5 ± 7.4	38.5 ± 7.1	37.5 ± 7.3	0.301
General health	45.9 ± 9.2	41.4 ± 8.3	43.7 ± 9	**0.028**
Vitality	46.5 ± 9.4	44.7 ± 9.3	45.6 ± 9.3	0.390
Social functioning	48.0 ± 11.6	48.7 ± 10.1	48.3 ± 10.8	0.966
RL – emotional problems	48.8 ± 12.9	51 ± 9.5	49.9 ± 11.3	0.500
Mental health	51.4 ± 7.7	52.8 ± 8.1	52.1 ± 7.9	0.315
Physical component summary	38.5 ± 8.4	36.7 ± 7.3	37.6 ± 7.9	0.150
Mental component summary	53.1 ± 10.3	54.4 ± 10.1	53.8 ± 10.1	0.477
Functional capacity				
6-minute walk test distance (m)	480 ± 94	516 ± 112	498 ± 104	0.126
Hemodynamics and anthropometrics				
Resting heart rate (bpm)	76 ± 14	69 ± 14	73 ± 14	**0.029**
Resting systolic BP (mmHg)	124 ± 17	127 ± 17	125 ± 17	0.536
Resting diastolic BP (mmHg)	78 ± 11	79 ± 11	78 ± 11	0.671
Height (cm)	162.8 ± 7.4	176.8 ± 5.5	169.8 ± 9.6	**<0.001**
Body mass (kg)	79.8 ± 21.6	92.9 ± 18.9	86.4 ± 21.2	**0.002**
Body mass index (kg/m^2)	29.9 ± 6.9	29.7 ± 5.7	29.8 ± 6.3	0.968
Waist circumference (cm)	93.6 ± 15.8	105.1 ± 15.0	99.6 ± 16.3	**0.002**
Body fat (%)	37.2 ± 7.7	25.9 ± 7.0	31.2 ± 9.2	**<0.001**
Anxiety and depression (n=20 females, n=35 males)				
Anxiety (points)	5.5 ± 3.2	4.4 ± 3.4	4.8 ± 3.3	0.151
Depression (points)	4.2 ± 4.2	4.2 ± 3.1	4.2 ± 3.5	0.474
Device-measured physical activity, min/week, (n=38 females, n=34 males)				
Light physical activity	2,243 ± 687	1,978 ± 574	2,118 ± 645	0.083
Moderate physical activity	137 ± 125	163 ± 155	149 ± 140	0.453
Vigorous physical activity	4.1 ± 10.3	4.1 ± 9.1	4.1 ± 9.7	0.819
MVPA	141 ± 132	167 ± 159	153 ± 145	0.440
Step counts per week	30,979 ± 18,524	30,771 ± 18,069	30,881 ± 18,182	0.752

Data: means ± standard deviations. P<0.05: significance. AF: Atrial fibrillation; BP: Blood pressure; FFM: Fat-free mass; MVPA: Moderate- to vigorous-intensity physical activity; RL: Role limitations; $\dot{V}O_{2peak}$: Peak aerobic power.

Hemodynamic and anthropometric measures. Females had a higher resting HR (F: 76±14 vs. M: 69±14 bpm, p=0.029), lower body mass (F: 79.8±21.6 vs. M: 92.9±18.9 kg, p=0.002), waist circumference (F: 93.6±15.8 vs. M: 105.1±15.0 cm, p=0.002), percent FFM (F: 62.8±7.7 vs. M: 74.1±7.0%, p<0.001) and FFM (F: 47.2±8.1 vs. M: 67.2±10.5 kg, p<0.001), and higher body fat (37.2±7.7 vs. 25.9±7.0%, p<0.001) than males (see Table 4.2.).

Anxiety and depression. Mental health data were reported by 20 females and 35 males from the Opportunity trial. The severity of anxiety and depression did not differ between sexes (see Table 4.2.). There was a low prevalence of elevated (>7 points) anxiety (F: 3 [15%] vs. M: 6 [17%], p=0.836) and depression (F: 3 [15%] vs. M: 3 [9%], p=0.462) across both sexes.

MVPA levels. Valid physical activity data were available in 38 females and 34 males (See Table 4.2.). No differences were observed between females and males in MVPA (141±132 vs. 167±159 minutes per week). Only 12 (32%) females and 8 (24%) males met the 200 weekly minutes of MVPA (χ2(1)=0.580, p=0.446); and 13 (34%) females and 14 (41%) males met the 150 weekly minutes of MVPA (χ2(1)=0.372, p=0.542).

Associations of $\dot{V}O_{2peak}$ with physical and mental health measures by sex. In females, $\dot{V}O_{2peak}$ (in mL O_2/kg/min) was positively associated with the PCS (p=0.026, r=0.361), several subscales of the SF-36 including physical function (p=0.020, r=0.30), role physical (p=0.033, r=0.348), general health (p<0.001, r=0.548) and role emotional (p=0.006, r=0.434), and 6MWT distance (p<0.001, r=0.671). $\dot{V}O_{2peak}$ was negatively associated with self-reported AF burden (p=0.038, r=-0.353), waist circumference (p=0.040, r=-0.353) and depressive symptoms (p=0.018, r=-0.523). In males, $\dot{V}O_{2peak}$ was positively associated with the PCS (p=0.001, r=0.536), physical function (p=0.027, r=0.359), vitality (p=0.028, r=0.362) and 6MWT distance (p<0.001, r=0.552). $\dot{V}O_{2peak}$ was negatively associated with age (p=0.030, r=-0.352) and waist circumference (p=0.010, r=-0.425).

Associations of MVPA with physical and mental health measures by sex. In females, MVPA levels were positively associated with $\dot{V}O_{2peak}$ ($p<0.001$, $r=0.612$), three subscales of the SF-36 including physical function ($p=0.037$, $r=0.345$), vitality ($p=0.006$, $r=0.438$) and role limitations due to emotional problems ($p=0.014$, $r=0.401$), and 6MWT distance ($p=0.001$, $r=0.539$). MVPA levels were negatively associated with age ($p=0.025$, $r=-0.363$) and depressive symptoms ($p=0.028$, $r=-0.502$). In males, MVPA levels were positively associated with $\dot{V}O_{2peak}$ ($p<0.001$, $r=0.596$), PCS ($p<0.001$, $r=0.671$), three subscales of the SF-36 including physical function ($p=0.009$, $r=0.440$), role limitations due to physical problems ($p=0.043$, $r=0.349$) and vitality ($p=0.036$, $r=0.367$), 6MWT distance ($p=0.011$, $r=0.429$) and resting HR ($p=0.046$, $r=-0.344$). MVPA levels were negatively associated with patient-reported number of visits to the emergency department ($p=0.034$, $r=-0.369$).

4.6. Discussion

The worse prognosis of females with AF may derive from a poorer health profile and health behaviours than their male counterparts. We conducted a comprehensive comparison of physical and mental health characteristics, and health behaviours, between females and males with persistent and permanent AF (see Figure 4.1. for a visual summary). Besides a greater proportion of males being prescribed statins, there were otherwise no sex differences in sociodemographic and gender-related factors, medical conditions nor medications.

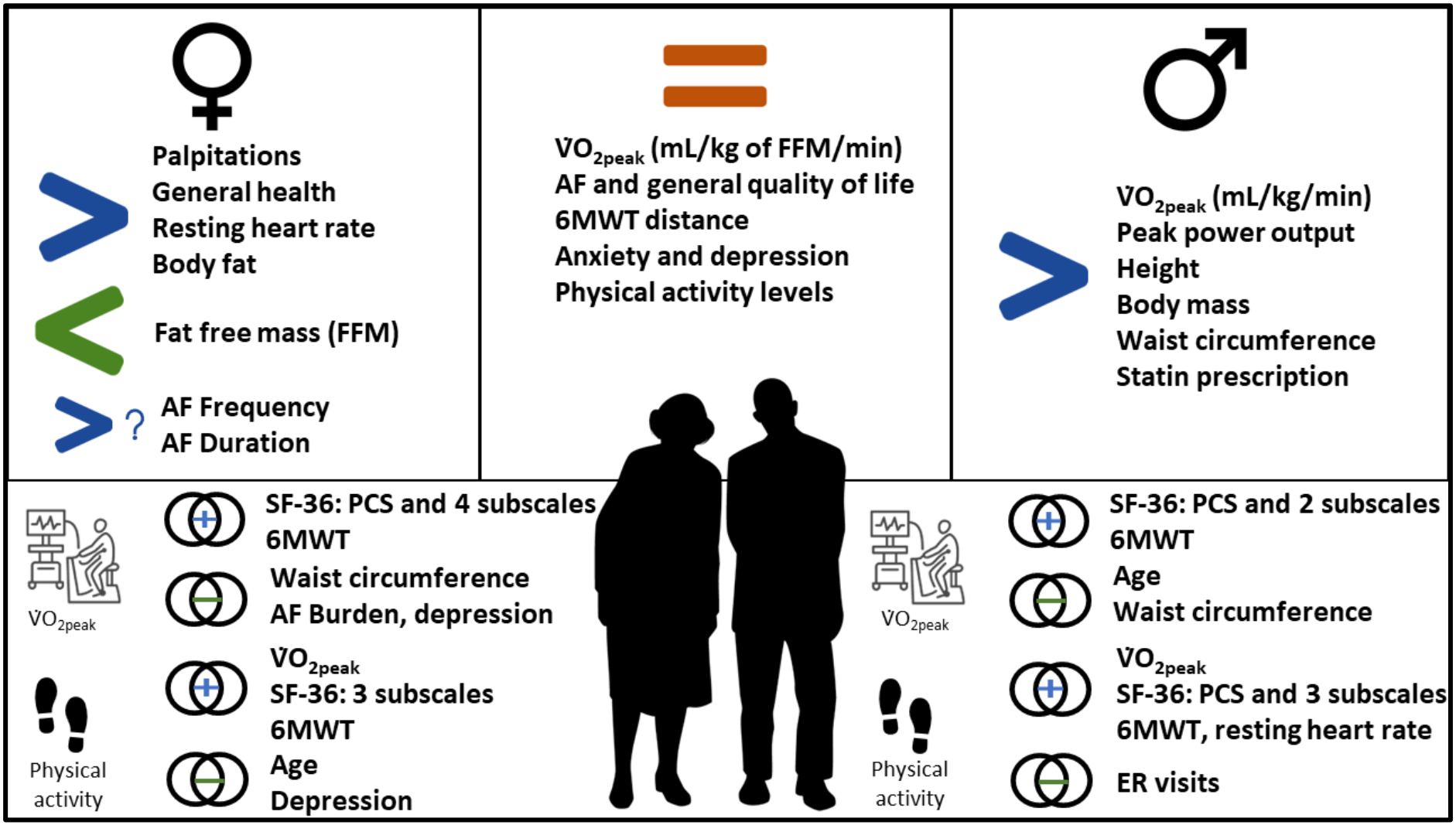

Figure 4.1. Visual representation of sex differences in physical and mental health characteristics in patients with persistent and permanent atrial fibrillation. The bottom portion of the figure represents associations of $\dot{V}O_{2peak}$ and MVPA levels with health characteristics in each sex separately. (>): Higher than the other sex; (<): Lower than the other sex; (=): No sex differences; (+): positive association; (-): negative association. 6MWT: 6-minute walk test; AF: Atrial fibrillation; ER: Emergency department; FFM: Fat-free mass; PCS: Physical component summary score; SF-36: Medical outcomes short-form 36; $\dot{V}O_{2peak}$: peak aerobic power.

Consistent with our hypothesis, relative $\dot{V}O_{2peak}$ adjusted for body mass was significantly lower in females than males, with a 4.5 mL O_2/kg/min (27%) sex difference. However, adjusting for FFM narrowed the gap to 1.8 mL O_2/kg of FFM/min (7%), such that the relative $\dot{V}O_{2peak}$ was no longer different between sexes. These findings suggest that sex differences in $\dot{V}O_{2peak}$ in patients with AF are largely mediated by differences in body size and composition. In our study, the mean FFM was 20 kg lower in females who, in turn, had a 11% higher mean body fat when compared to males with AF. In the general population (55-74 years old), the validity of $\dot{V}O_{2peak}$ adjusted by FFM has been shown to be higher than when adjusted by body mass, as the latter may underestimate $\dot{V}O_{2peak}$ in individuals with obesity.[46] Previous literature comparing $\dot{V}O_{2peak}$ adjusted by FFM between sexes has predominantly included healthy younger adults (<40 years old), making comparisons with the AF population difficult.[32] In patients with CVD entering CR who performed a CPET on a cycle ergometer (n=83, 23% females), females had a 6.0 mL O_2/kg/min (31%) and 2.7 mL O_2/kg of FFM/min (9%) lower $\dot{V}O_{2peak}$ than males; the latter remained significantly different between sexes (p=0.042).[76] A lower concentration of hemoglobin in the blood is another proposed mechanism for females' lower $\dot{V}O_{2peak}$, as it impacts key components of the Fick equation by diminishing the oxygen content of the arterial blood and the maximal arterio-venous oxygen content difference.[32] Further, in highly trained athletes, females have been shown to have smaller heart and cavity sizes, lower wall thickness and left ventricle mass than males.[77,78] This may diminish females' stroke volume and subsequent $\dot{V}O_{2peak}$. After normalizing by body surface area, females' heart size was no longer smaller than those of male athletes.[77,78] Such sex differences may also apply to patients with AF, although further investigation is needed.

The sex gap in $\dot{V}O_{2peak}$ adjusted for body mass may be larger in patients with AF (our study: 4.5 mL O_2/kg/min lower in females; CopenHeartRFA trial: N=210, 28% females: 7.5

mL O_2/kg/min lower $\dot{V}O_{2peak}$ in females[34]) than other CVD conditions (N=5,396, 25% females: 3.8 mL O_2/kg/min lower $\dot{V}O_{2peak}$ in females[79]). Sex comparisons with a larger sample across different diagnoses are warranted. Although the ACSM classification categories were created based on healthy adults, the high (F:72%, M: 79%) prevalence of *very poor* $\dot{V}O_{2peak}$ is concerning given its prognostic value. The 4.5 mL O_2/kg/min sex difference in our study also remains concerning, as it may translate into a greater risk for CVD morbidity and mortality in females.[31]

Thirty three percent more females than males reported palpitations; this may be related to females' faster resting HR (F: 76 vs. M: 69 bpm). In other studies where a 10% to 25% greater proportion of females than males reported palpitations, some[22,38] but not all[21,35,39] found a faster resting HR in females than males. Contrary to our hypothesis, the frequency (F: 2.1±1.7, M: 1.4±1.1 points, p=0.053) and duration of AF episodes (F: 2.5±2.5, M: 1.7±2.0 points, p=0.083) did not differ between sexes. A study appropriately powered to examine sex differences in these secondary measures may have revealed statistically significantly greater AF symptoms in females. If those sex differences were present, it could partly mediate females' greater reporting of palpitations. Interestingly, a systematic review found that females may be more symptomatic even when AF burden does not differ between sexes.[80] Conflicting with our findings, additional sex differences in patient AF symptoms have been found by others, including greater reporting by females of dizziness,[21,22,34] dyspnea[21] and fatigue.[21,22,35] Since Study 3 includes patients who are about to start an exercise program, and patients with AF who are more symptomatic report greater fear of movement,[81] selection bias may have attracted less symptomatic females. The AFSS median symptom score (range 0 to 35) implies that patients were low-to-moderately symptomatic (F: 8, 95% CI 6 to 11 points; M: 7, 95% CI 6 to 8 points), in line with median data from other observational studies (5, 95% CI 5 to 6 points)[82] and RCTs (6, interquartile range 3 to 12 points)[83] in patients with AF.

QoL is an important patient-reported outcome, and is diminished in those with AF when compared to healthy[84] and other CVD[85] populations. Contrary to our hypothesis, females reported a 4.5 point significantly higher general health score than males. The reasoning for this is unclear, as there were otherwise no sex differences in the SF-36 subscales. The only systematic review in patients with AF comparing QoL between sexes found that six studies reported lower PCS scores in females than males across several AF subtypes.[80] We did not observe such sex differences. Our mean PCS score (37.6 ± 7.9 points) was 12 and 7 points lower than reported by other females and males with AF, respectively, and 16 and 13 points lower than non-AF adults.[86] In contrast, our mean MCS score (53.8 ± 10.1 points) was similar to other patient groups with and without AF.[86] The low $\dot{V}O_{2peak}$ in more than two thirds of our patients, and the poor functional capacity observed in more than one third of females and males may have led to low PCS scores. Strategies to enhance self-perceived physical health (e.g., exercise training) may be warranted in patients with AF.

Discordant with our hypothesis, functional capacity did not significantly differ between sexes. In a sub-study of the AFFIRM trial (N=245 patients with AF, 33% females), females treated with heart rhythm or rate control strategies walked on average 57 metres less than males; this sex difference was significant and 20 metres greater than in our study.[87] Wagner *et al*. reported an 85 to 104 lower 6MWT distance (metres) in females than males with paroxysmal and persistent AF following an ablation (N=210, 28% females).[34] Females with poor functional capacity may have been less likely to enrol in our exercise studies, hence the small sex difference observed (36 metres lower 6MWT distance in females).

The clustering of CVD risk factors is associated with adverse events[24] and poorer patient QoL.[88] More risk factors have been previously reported in females than males with AF (3.7±1.2 vs. 2.9±1.4, $p<0.001$).[88] Thus, our comprehensive sex-specific examination of several CVD risk factors is of clinical relevance. No sex differences were observed in the

proportion of females and males who were overweight, affected by obesity or with a high-risk waist-circumference. Scarce literature suggests that a greater proportion of females than males with AF experience obesity (50% vs. 37%, p=0.033[35], 40% vs. 27%, p<0.001[38]), yet in our study obesity was highly prevalent in both females (46%) and males (41%). The observed differences in anthropometrics (i.e., lower height, body mass, waist circumference in females) and hemodynamics (i.e., faster HR in females) align with our hypotheses, and in other studies in those with AF[22] and CVD.[89] Body composition is rarely assessed in patients with AF, hindering comparisons. Similar to our findings, a 20 kg lower FFM was observed in females than males with CVD.[76] This warrants attention as a high-muscle and low-fat body composition phenotype is associated with the lowest mortality risk in patients with CVD.[90] Thus, females with AF may benefit from lifestyle interventions such as exercise training to build muscle mass and narrow the sex differences in body composition. Interestingly, a sex dimorphism in the general population has been suggested such that higher total fat, leg fat and trunk fat may be protective against CVD risk in females only.[90] This merits further investigation in adults with AF. Addressing the high prevalence of CVD risk factors in both sexes should be a priority as previous research has shown that a greater number of CVD risk factors in females compared to males with permanent AF was a major contributor for their higher yearly cardiovascular event-rate (8% vs. 5% p=0.03).[88] Further, for every risk factor, the PCS score of the SF-36 has been shown to decrease by 1.4 points (95% CI -2.7 to -0.5) in females, and by 1.21 points (95% CI -1.9 to -0.5) in males (p<0.05).[88]

The prevalence and consequences of poor mental health remain misunderstood in patients with AF, as most of the psychological literature has focused on how anxiety and depression may increase the risk of AF, and not as much has been explored in those who have an AF diagnosis. Anxiety and depression have been linked with greater symptom burden,[91] poorer QoL[92] and a heightened risk for AF recurrence.[93] The prevalence of elevated anxiety

(16%) and depression (11%) in Study 2 was lower than reported by other studies in patients with AF, where typically 30 to 35% report anxiety and 20 to 30% report depression.[8,93,94] In contrast to our hypothesis, our anxiety and depression scores did not differ between sexes, yet they were consistent with those of Wagner *et al.*, who did not observe differences between sexes in patients with AF entering CR (females: A: 5.1±3.6; D: 3.2±3.5 points vs. males: A: 5.7±4.0; D: 3.3±3.2 points). As previously surmised, patients who agree to participate in exercise and CR may have a better mental health than the general AF population.

Higher self-reported physical activity levels have been shown to lower the risk of AF progression,[95] major adverse cardiovascular events, and all-cause and cardiovascular death in patients with AF.[96,97] This may be more pronounced with vigorous than moderate-intensity physical activity.[96] Sex differences in habitual levels of physical activity could explain our observed sex differences in $\dot{V}O_{2peak.}$ However, discordant with our hypothesis, the 26-min lower weekly device-measured MVPA in females than males did not reach significance. Approximately one third of patients were meeting 150-200 minutes per week of MVPA, without differences between sexes. Our findings can be compared to very few studies, most of which used self report surveys and did not stratify their findings by sex.[35,71,98,99] In the SAFETY trial (n=335, 48% female), 37% of females and 56% of males with AF self-reported engaging in ≥150 minutes per week of MVPA (p=0.001).[35] Greater proportions of active patients have been found by others, for instance, 67% of patients with persistent AF self-reported meeting ≥150 weekly MVPA minutes at CR entry (n=119, 21% female).[98] When using accelerometers, 73% and 63% of patients met ≥150 and ≥200 weekly MVPA minutes, respectively, yet it was a younger sample with predominantly paroxysmal AF (n=30, 40% female).[71] Our device-measured weekly minutes of MVPA are lower (mean: 153 minutes per week) than previously reported, although results have been heterogeneous ranging between 164 to 334 weekly minutes.[71,99] Further, our 30,000 steps per week (~4,286 steps per day) are

similar to those previously reported in patients with permanent AF (n=96, 29% females).[99] Physical activity is a modifiable behaviour that should be targeted to positively impact the health of patients with AF, as many (24 to 41%) females and males with AF do not meet the recommended levels.

Associations of $\dot{V}O_{2peak}$ and MVPA with other measures. In both sexes, there was a strong ($r \geq 0.5$) positive association between $\dot{V}O_{2peak}$ and measures of patient reported general QoL and functional capacity, and a moderate negative association with waist circumference. Similarly, a strong, positive association between MVPA levels and $\dot{V}O_{2peak}$, patient reported general QoL and functional capacity was observed. The inability to establish a temporal sequence in this cross-sectional examination precludes inferring causality, yet these associations set the stage for future research exploring whether interventions that lead to increases in $\dot{V}O_{2peak}$ and MVPA levels may, in turn, improve QoL and functional capacity in this population.

Strengths and limitations

This study has several strengths. An equal number of females and males were included following an *a priori* sample size calculation for the primary outcome. This methodology is recommended by the SAGER guidelines, yet is rarely implemented as sex-based analyses are often an afterthought.[41,100] Since AF impacts several aspects of patients' wellbeing, we conducted a comprehensive examination that included critical patient-reported outcomes, as well as device-measured $\dot{V}O_{2peak}$ and MVPA levels that minimized social desirability bias. On the other hand, the study has several limitations. The cut-points used to establish different physical activity intensities have not been validated in patients with AF. Different methodological recommendations have been proposed to determine physical activity behaviours with accelerometers.[69,101–103] There has been substantial cut-point heterogeneity in

the literature, warranting further validation work. For instance, lower cut-points may be more appropriate for older adults (e.g., MVPA ≥1,041 counts/min) who may expend more energy expenditure to complete a task.[102] Despite our diverse recruitment strategies, all our participants had qualified for inclusion and volunteered for an exercise trial, thus, selection bias may have attracted a healthier and less symptomatic set of patients. This may limit the generalizability of our findings. Finally, for our secondary outcomes, the absence of evidence for sex differences may not necessarily imply evidence of absence, particularly for anxiety and depression as a smaller number of participants reported on this measure.

4.7. Conclusion

$\dot{V}O_{2peak}$ adjusted for body mass was 27% lower in females than males with AF. Adjusting for FFM narrowed the gap to a non-significant 7% sex difference. The 11% greater body fat and lower FFM in females than males with AF may largely influence sex differences in $\dot{V}O_{2peak}$. A greater proportion of females reported palpitations, they had a higher resting HR, and better general health than males. Several modifiable risk factors including low $\dot{V}O_{2peak}$, obesity, high-risk waist circumference and low MVPA levels were highly prevalent in both sexes, highlighting a need for lifestyle strategies; these may also mitigate sex differences in symptoms and physical health. Continued efforts are needed to improve our understanding of sex differences in the modifiable health factors and behaviours in patients with AF.

4.8. References

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4.9. Supplemental material

Appendix 4.1. – Strengthening the reporting of observational studies in epidemiology (STROBE): Checklist of items that should be included in reports of cross-sectional studies.

Section	Item N.	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		I Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix 4.2. – Sample size calculations to test the hypothesis of whether females would present with lower $\dot{V}O_{2peak}$ than males with persistent and permanent atrial fibrillation.

t tests - Means: Difference between two independent means (two groups)			
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0.7
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	2.8861739
	Critical t	=	1.9965644
	Df	=	66
	Sample size group 1	=	34
	Sample size group 2	=	34
	Total sample size	=	**68**

CHAPTER 5 – Sex differences in changes in physical and mental health outcomes following exercise training in patients with persistent and permanent atrial fibrillation

PREAMBLE TO STUDY 3

The notable clinical sex differences in atrial fibrillation (AF), such as females being more symptomatic than males, may warrant the consideration of sex when examining the efficacy of exercise programs. However, sex-based analyses are rarely conducted in exercise trials, and females are underrepresented. This study includes original data collected across two randomized clinical trials (*Opportunity: Exercise training in patients with atrial fibrillation – addressing clinical needs;* and, *Exercise-AF: Exercise training in patients with persistent and permanent atrial fibrillation*) regarding potential differences over time in physical and mental health outcomes, and behaviours between females and males following a 12-week exercise program.

5.1. Abstract

Background: Exercise training (ET) improves peak aerobic power ($\dot{V}O_{2peak}$), a predictor of AF recurrence and mortality, in patients with atrial fibrillation (AF). Some studies suggest females (F) may experience smaller gains in $\dot{V}O_{2peak}$ than males (M) following ET. **Aim:** To compare changes in $\dot{V}O_{2peak}$ (primary) and additional physical and mental health outcomes between F and M with AF following 12 weeks of ET. **Methods:** Data from two RCTs were used. Patients with persistent and permanent AF were randomized to supervised biweekly 23-minute high-intensity interval training or 60-minute moderate- to vigorous-intensity continuous training on a cycle ergometer. $\dot{V}O_{2peak}$ (exercise test to exhaustion), AF-specific and general quality of life (QoL), functional capacity (6-minute walk test [6MWT]), resting heart rate (HR), blood pressure, anthropometrics, anxiety, depression and device-measured physical activity levels were collected at baseline and 12 weeks. Linear mixed-models were used to test the effects of time, sex and their interaction. **Results:** We included 34 F and 77 M (31% F, F: 71±8 vs. M: 68±8 years old, p=0.25). Effects of time (p=0.011) and sex (p<0.001) showed improvements in $\dot{V}O_{2peak}$ and a lower $\dot{V}O_{2peak}$ in F. $\dot{V}O_{2peak}$ increased in F (median [95% CI]: 14.3 [13.3 to 15.1] to 16.9 [12.2 to 21.5] mL O_2/kg/min; +18%]) and M (19.0 [17.5 to 20.8] to 21.1 [17.2 to 24.0] mL O_2/kg/min; +11%, interaction: p=0.707). Time effects showed improvements in AF-specific QoL (global well-being, total AF burden, symptom score), 6MWT, resting HR, waist circumference, anxiety and depression (p<0.05). Sex effects showed greater patient-reported AF frequency, duration and severity, higher HR and body fat, and lower body mass and waist circumference in F (p<0.05). PA levels did not improve over time nor differ by sex. **Conclusion:** Improvements in $\dot{V}O_{2peak}$ and several physical and mental health outcomes following 12 weeks of ET did not differ by sex. Only improvements in $\dot{V}O_{2peak}$ reached clinical significance.

5.2. Introduction

Exercise training is recommended for the management of patients with atrial fibrillation (AF), the most common sustained cardiac arrhythmia.[1–3] The 2020 Canadian Cardiovascular Society (CCS)/ Canadian Heart Rhythm Society (CHRS) guidelines for the management of patients with AF are the first to include specific exercise targets, recommending patients engage in at least 200 minutes per week of moderate-intensity aerobic exercise training, resistance training 2 to 3 days per week, and flexibility at least 2 days per week.[3] Many patients with AF have a heightened cardiovascular disease (CVD) risk factor profile, as they experience hypertension (60%),[4] anxiety and depression (30%),[5,6] and a markedly lower peak aerobic power ($\dot{V}O_{2peak}$) than other CVD populations (AF vs. non-AF in two previous studies: 14.6±3.1 vs. 19.6±5.1;[7] 16.9±5.2 vs. 20.2±5.5 mL O_2/kg/min[8]). The latter may contribute to the 3.7-fold increased risk of all-cause mortality in patients with AF when compared to the general population,[9] as a lower $\dot{V}O_{2peak}$ predicts a higher risk for AF recurrence,[10] CVD hospitalization and all-cause mortality.[11]

Several exercise programs implementing between 90 to 300 weekly minutes of low- to high-intensity exercise training of various modalities (e.g., walking, cycling, circuit training, slow movements), ranging from 6 weeks to 1 year, have led to statistically significant increases in estimated[12–15] and directly measured[7,8,16–19] $\dot{V}O_{2peak}$ across patients with different AF subtypes. Exercise training may be beneficial to manage patients with AF by improving their: (i) disabling symptoms of low exercise tolerance, dyspnea, lethargy and palpitations[20] (e.g., reductions in symptom frequency and severity have been reported following exercise training);[17,21] (ii) poor self-reported quality of life (QoL)[22] (some improvements in AF-specific QoL[14] and general QoL[15,17,18,21] have been noted); (iii) poor functional capacity,[20] which limits patients' ability to engage in activities of daily living (a 3 to 27% increase in six-minute walk test [6MWT]

distance[23–25]); (iv) heightened CVD risk factor profile, as CVD is the leading cause of death in patients with AF[9] (reductions in resting heart rate [HR],[8,13,15,26] percent body fat,[27] anxiety and depression[14,24]); and, physical activity levels (few increases in physical activity habits).[12,17,25]

AF can be sub-classified as paroxysmal, persistent, longstanding persistent and permanent based on the duration of the AF episodes.[3] Several differences have been noted among AF subtypes. Patients with persistent and permanent AF may report greater AF burden,[28] experience more co-morbidities,[29] more advanced cardiac remodelling,[30] and a heightened stroke risk than patients with paroxysmal AF.[30] Physical inactivity, [29] obesity[28] and smoking[29] have also been shown to be more prevalent among those with persistent and permanent AF, when compared to patients with paroxysmal AF. Thus, patients with persistent and permanent AF appear to be in the greatest need for improved quality of care and may benefit the most from lifestyle-based therapies that address their heightened CVD risk factor profile.

Several clinical sex differences exist in patients with AF. Females with AF generally demonstrate worse physical and mental health than males,[31] with a lower $\dot{V}O_{2peak}$,[32] more frequent and severe AF symptoms,[33–35] a 24% lower QoL after co-morbidity adjustment,[36] greater symptoms of anxiety and depression,[37] and lower physical activity levels.[38] Such sex differences may influence the chronic responses of females and males with AF to exercise training. In healthy and CVD populations, whilst several studies have shown that females improve $\dot{V}O_{2peak}$ to a lesser extent than males following the same exercise program,[39–43] some trials did not observe differences between sexes.[43–45] These sex-based comparisons are yet to be examined in patients with AF. Further, much less is known about the potential sex differences in changes in additional CVD risk factors (e.g., blood pressure, body mass index [BMI], anxiety, depression) following exercise training.[32] The scarce sex disaggregation of research findings,

combined with the severe female under-representation in exercise trials (<30% of AF participants are females),[46] leads to females with AF receiving exercise recommendations without appropriate supporting evidence.[47–49]

5.3. Objectives and hypotheses

The primary purpose was to compare changes in $\dot{V}O_{2peak}$ between females and males with persistent and permanent AF following 12 weeks of exercise training. It was hypothesized that females with AF would demonstrate a smaller $\dot{V}O_{2peak}$ improvement than males. The secondary aim was to compare changes in additional physical and mental health outcomes (i.e., AF symptoms, QoL, functional capacity, hemodynamic and anthropometric measures, anxiety, depression) and health behaviours (i.e., device-measured levels of moderate-to vigorous-intensity physical activity [MVPA]) between sexes following 12 weeks of exercise training.

5.4. Methods

Study design and setting

Data from two single-center, parallel-group, randomized controlled trials (RCTs), Opportunity (ClinicalTrials.gov #NCT02602457) and Exercise-AF (ClinicalTrials.gov #NCT03397602), were used. The studies were conducted at the University of Ottawa Heart Institute (UOHI), a tertiary care cardiovascular centre located in Ontario, Canada. The Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed (see Appendix 5.1.).[50] The Sex and Gender Equity in Research (SAGER) guidelines were also considered.[51] Approval was obtained from the Ottawa Health Science Network Research Ethics Board (protocol #: 20150427; protocol #: 20180342).

Participants

Participants were recruited between November 2015 and 2022 (this end date was selected given the student's timeline; Exercise-AF trial recruitment is ongoing). Sources of recruitment included referrals from UOHI physicians, screening of the UOHI's electronic medical records, or through the distribution of posters and newsletters to several community and medical centres within the National Capital Region of Canada. All participants provided written, informed consent. Eligible patients included those who: (1) had persistent or permanent AF as confirmed by a physician; (2) were rate-controlled with a resting HR ≤110 bpm; (3) were able to perform a cardiopulmonary exercise test (CPET) to volitional exhaustion; (4) were ≥40 years of age; and (5) were able to read and understand English or French. Patients were excluded if they: (1) were participating in exercise training >2 days per week; or, (2) had a diagnosis of unstable angina, uncontrolled diabetes mellitus, severe mitral or aortic stenosis, or hypertrophic obstructive cardiomyopathy.

Screening

Study staff screened potentially eligible participants. Patients completed a medical assessment with a UOHI physician to confirm their eligibility criteria and appropriateness for the RCTs. The presence of AF in each patient was verified by the physician by pulse and with a 24-hour Holter monitor (DR200/HE Holter and Event Recorder, NorthEast Monitoring, Inc, Maynard, MA). Sex (i.e., legal sex assigned at birth), age and medical information were retrieved from the UOHI's medical records.

Baseline visit

Once eligibility was confirmed, two baseline visits were scheduled. Participants' sociodemographic and gender-related factors (i.e., ethnicity, level of education, employment status, personal income) and prescribed medications were self-reported by patients. Study staff collected participants' resting HR and blood pressure, height, body mass, waist circumference and body composition. For the latter, participants were given pre-testing guidelines for bioelectrical impedance testing to minimize variability due to external factors (e.g., avoid electrolyte imbalance),[52,53] including: (i) no eating or drinking for 4 h; (ii) no MVPA for 12 h; (iii) no alcohol consumption for 48 h; (iv) to void their bladder within 30 min; and, (v) to refrain from consuming caffeine and non-prescribed diuretic use for 12 h. Participants also completed a supervised 6MWT, questionnaires and received an accelerometer to wear for 7 days with a 24-hr wear-time journal to record physical activity levels. On the second visit, participants underwent a CPET to volitional exhaustion (see $\dot{V}O_{2peak}$ section).

Randomization

Participants from the Opportunity trial were randomized in a 1:1 ratio to high-intensity interval training (HIIT) or moderate- to vigorous-intensity continuous training (MICT). Participants from the Exercise-AF trial were randomized in a 1:1:1 ratio to HIIT, MICT or standard care (control). Those in the control group were not included in this Study 3 as our aim was to compare the effects of exercise training between sexes. The UOHI Cardiovascular Research Methods Centre, an independent group to these studies, performed the randomization using a balanced block, stratified by AF type (i.e., persistent or permanent), random sequence generated with a computer. Treatment assignments were placed in sealed, numbered opaque envelopes to ensure concealment until all baseline measures were completed and to minimize performance bias.

Exercise intervention

Participants attended biweekly supervised exercise training sessions for 12 weeks at the Cardiac Prevention and Rehabilitation Centre of the UOHI. Participants in both HIIT groups and in the MICT group of the Exercise-AF trial used a cycle ergometer for their sessions (True Fitness, CS200, St. Louis, Mo, United States). A maximum of two participants exercised simultaneously under the supervision of study staff. Their exercise prescription was based on a percentage of the peak power output (PPO) achieved during the baseline CPET. In contrast, the MICT group of Opportunity was part of a standard cardiovascular rehabilitation (CR) class, as such, participants used various aerobic equipment (e.g., cycle ergometer, elliptical, jog/walk on the track) and exercised in a larger group (10 to 15 people) under the supervision of a physiotherapist and a nurse. Their exercise prescription was based on a percentage of the HR_{peak} achieved during the baseline CPET and/or a range of ratings of perceived exertion (RPE).

HIIT: The 23-minute HIIT sessions consisted of a 2-minute warm-up at 50% of PPO; 16 minutes of conditioning (2 x 8-minute interval training blocks of 30-second work periods at 80%-100% of PPO interspersed with 30-second active recoveries, with 4 minutes of recovery between the 2 blocks); and a 1-minute cool-down at 25% of PPO. The power output (W) was gradually increased for the first two weeks until patients were able to exercise within the range or as close to their prescribed % of PPO. To adjust for improvements in exercise tolerance over the 12 weeks, patients in the Opportunity trial were able to increase to 150% of their PPO, and in the Exercise-AF trial, patients completed a 6-week CPET and their 80 to 100% of PPO was adjusted accordingly. HR (using values displayed on Polar HR monitors [Polar RS800CX, Polar Electro Oy, Kempele, Finland] or the cycle ergometer) and RPE using the 6 to 20-point Borg scale[54]

were recorded by staff before, during and 5 minutes following the sessions. The power output during exercise was recorded by staff (see Appendix 5.2. for details).

MICT: *(1) Opportunity trial:* The 45- to 60-minute sessions in the Opportunity trial followed standard CR guidelines, consisting of a 15-minute warm-up; 30 minutes of continuous aerobic conditioning at 67 to 95% of HR_{peak} and 12 to 16 points (somewhat hard to hard) of RPE; and a 15-minute cool-down of strengthening and stretching exercises. The duration of the conditioning part increased from 15 to 30 minutes over the 12 weeks. HR (using values displayed on Polar HR monitors [Polar RS800CX, Polar Electro Oy, Kempele, Finland] or the aerobic equipment) and RPE were recorded by patients in their CR exercise logs after the 30-minute conditioning and verified by CR staff (Appendix 5.2.). *(2) Exercise-AF trial:* The 60-minute sessions in the Exercise-AF trial consisted of a 10-minute warm-up at 50% of PPO; 40 minutes at 60% of PPO; and a 10-minute cool-down at 25% of PPO. To account for possible improvements in exercise tolerance, patients completed a 6-week CPET and their prescription was adjusted accordingly. HR (using values displayed on Polar HR monitors [Polar RS800CX, Polar Electro Oy, Kempele, Finland] or the cycle ergometer) and RPE were recorded by staff before, during and 5 minutes following the sessions. The power output during exercise was recorded by staff (Appendix 5.2).

Follow-up

The baseline measures were repeated within one week of completing the 12-week exercise program. Whenever possible, research staff blinded to treatment allocation collected follow-up data. Physical activity levels were measured before and during the last week of the exercise program.

Primary outcome

Peak aerobic power ($\dot{V}O_{2peak}$)

$\dot{V}O_{2peak}$ was measured using an incremental CPET to volitional exhaustion (2-minute warm-up at 40 W, 20 W-increment per minute, 3-minute cool-down at 40 W) on an electronically-braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany; or Cosmed, US). The test was supervised by certified study staff (e.g., Clinical Exercise Physiologists) or cardiac stress technologists from the Department of Cardiac Imaging at the UOHI. RPE were reported every minute using the 6-20 Borg scale[54] to determine the level of perceived effort. Gas exchange was continuously monitored throughout the test using a metabolic cart (Oxycon Mobile, Carefusion; or Sensormedics Vmax, Yorba Linda, CA, United States). The highest 10- or 20-second average of oxygen uptake in mL O_2/kg/min represented $\dot{V}O_{2peak}$. A higher $\dot{V}O_{2peak}$ denotes a better cardiorespiratory fitness and is considered a clinical vital sign.[55] A minimal clinically important difference (MCID) for $\dot{V}O_{2peak}$ has not been established, yet an increase in directly measured $\dot{V}O_{2peak}$ of at least 1.75 mL O_2/kg/min has been previously used to indicate clinical significance in healthy adults and those with chronic cardiometabolic conditions, including patients with CVD.[56,57] In support, achieving such an increase has been shown to reduce AF recurrence and mortality by 5% to 10%.[10,11] To account for differences in body composition between sexes, $\dot{V}O_{2peak}$ was further adjusted for fat-free mass (FFM).[58] The proportion of patients within the different cardiorespiratory fitness categories (i.e., *very poor, poor, fair, good, excellent, superior*) according to the American College of Sports Medicine (ACSM) classifications for the general population were determined.[59] $\dot{V}O_2$ values during exercise on a cycle ergometer from the Oxycon Mobile and Cosmed devices have been shown to closely agree with those measured using the gold-standard Douglas bag method over a wide range of exercise intensities (e.g.,

during submaximal exercise intensities the $\dot{V}O_2$ difference between the systems was -1.3% to +2.6%, whereas at $\dot{V}O_{2max}$ 1.4% lower values were noted in the Oxycon, $p>0.05$) in healthy adults (n=60 adults, 3% females, 30±5 years old;[60] n=32 males, 23±4 years old[61]). Further, $\dot{V}O_{2peak}$ measured with a CPET has shown excellent test-retest reliability (Intraclass correlation coefficient [ICC]: 0.95, 95% CI 0.92 to 0.97) in patients with cardiac and respiratory conditions.[62,63] All participants had a baseline CPET. The collection of a follow-up CPET started approximately half-way through the Opportunity trial (as additional funding was then awarded for such testing) and was available for the Exercise-AF trial.

Secondary outcomes

AF symptoms

AF symptoms were self-reported by patients using the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale (CCS-SAF),[64,65] a simple, 3-step scale using closed questions (yes/no), comprising: (1-S) identification of AF-related symptoms (i.e., palpitations, dyspnea, dizziness, presyncope or syncope, chest pain, weakness or fatigue, other); (2-A) determination of the correlation between patient symptoms and AF rhythm (i.e., *is AF, when present, associated with the above-listed symptoms?*); and, (3-F) assessment of the impact of these symptoms on patient's daily functionality. The CCS-SAF has been validated against the University of Toronto Atrial Fibrillation Severity Scale (AFSS)[66] and the Medical Outcomes Study Short-Form (SF-36)[67] questionnaires, yet studies assessing the test-retest reliability or inter-rater reliability of this scale are lacking.[64]

AF-specific QoL

AF-specific patient QoL was measured using the AFSS questionnaire,[66] a widely used self-report survey assessing subjective and objective ratings of AF burden. *Part A*: overall well-being is rated on a 1 (worst possible life) to 10 (best possible life) visual analogue scale; and four items lead to the AF burden score (0-30) including the frequency, severity and duration of symptomatic patient AF episodes. *Part B*: four items assess healthcare utilization in the previous year. *Part C*: seven items assess patient symptom severity over the past 4 weeks, each are scored from 0 ("very little") to 5 ("a great deal"), leading to a symptom severity score between 0 to 35 points. For the overall well-being, higher scores denote better perceived health, and for the other sections of the AFSS, higher scores indicate greater AF burden. A change in the AFSS symptom score by at least 3 points has been previously considered clinically significant.[68] The psychometric properties of the AFSS have not been evaluated,[66] yet it has been shown to be sensitive to change.[69]

General QoL

General patient QoL was measured using the SF-36 v.1,[67] a 36-item self-report survey assessing general health over the previous 4 weeks. The SF-36 yields an 8-scale profile of functional health and well-being scores (i.e., physical functioning; role limitations due to physical problems; bodily pain; general health perceptions; energy/vitality; social functioning; role limitations due to emotional problems; mental health) as well as psychometrically-based Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Higher scores denote better perceived health.[70,71] The MCID for the PCS and MCS is estimated to be a change of at least 5 points.[72] The SF-36 is widely validated in CVD populations[73,74] and has been used in patients with AF.[70,71] In patients with a previous myocardial infarction (n=421, 66% males, 66±10 years

old), items in the same domain of the SF-36 have shown good internal consistency (Cronbach's $\alpha \geq 0.80$) and the SF-36 subscales have moderate-to-high (r=0.52 to 0.73) correlation with those of the Nottingham Health Profile survey, a QoL survey intended for primary care.[73] The reliability of the SF-36 remains unclear, with some studies suggesting some of the subscales are not responsive to the effects of CR programs,[75] and others showing better reliability in the individual subscales than the summary scores.[75,76] Its validity and ability to detect changes in perceived health over time has not been established in patients with AF.[75]

Functional capacity

Functional capacity was measured with the six-minute walk test (6MWT) distance in metres. Participants were instructed to walk on an indoor track as far as possible for 6 minutes. Walking a longer distance denotes better functional capacity. A 25- to 54-metre change has been considered a MCID for patients with cardiorespiratory conditions.[77,78] For this study, a conservative MCID of 54 metres was used. In patients with AF, walking a distance shorter than 450 metres has been associated with increased patient symptom burden,[79] thus, this cut-off was used to define patients with a low functional capacity. The 6MWT is a valid, practical field test commonly used in CR settings.[80] In CR participants, the 6MWT has shown moderate-to-high correlation (r=0.56 to 0.93) with $\dot{V}O_{2peak}$, is able to detect change in clinical status over time, and has good reliability (ICC: 0.97), although a 2 to 8% learning effect has been noted.[80]

Hemodynamic measures

Resting HR and blood pressure were collected in a seated position using an automated HR and blood pressure sphygmomanometer monitor (Welch Allyn, Canada) following standard

procedures.[59] Patients remained seated for 5 minutes prior to the measurement and were asked to keep their feet flat on the ground without crossing their legs. Three measurements were taken with at least 2 minutes in between, and the average was calculated and used for statistical analyses.[59]

Anthropometric measures

Body mass was measured using a digital scale (Health o meter® Heavy Duty Remote Digital Scale 752KL or Omron HBF-514C) to the nearest 0.1 kg and height was measured using a SECA 206 height measuring system to the nearest 0.1 cm. BMI was calculated based on the body mass and height (kg/m^2). Waist circumference was measured at the midpoint between the lower costal margin and iliac crest while patients stood with arms at the sides, feet shoulder width apart and abdomen relaxed after a full exhalation using a SECA 201 tape measure to the nearest 0.1 cm.[59] Triplicate measurements were taken, and the average was used for analyses. Proportions of participants across several BMI (underweight: <18.5 kg/m^2, normal: 18.5 to 24.9 kg/m^2; overweight: 25.0 to 29.9 kg/m^2, obesity ≥30 kg/m^2) and high-risk waist circumference (females: ≥88 cm; males: ≥102 cm) categories were calculated.[59]

Body composition was measured using a digital scale (Tanita FitScan UM-041F, Omron HBF-514C), which estimates percent body fat by hand-to-foot bioelectrical impedance analyses to the nearest 0.1%. Participants were instructed to step barefoot on the scale, stand upright, hold the display unit with both hands and extend the arms parallel to the floor for 5-10 seconds. Body mass and percent body fat were used to calculate FFM (body mass – [body mass × % body fat/ 100]). These scales have shown good validity and reliability (Tanita and Omron: r>0.8) in the

general population,[53,81] including an ability to detect changes in body composition in clinical populations over time.[82]

Anxiety and depression symptoms

Patient symptoms of anxiety and depression over the previous week were measured using the 14-item Hospital Anxiety and Depression Scale (HADS).[83] Each item is rated on a 4-point scale (0-3 points). It yields separate anxiety and depression scores (7 items each); the subscale scores range from 0-21 points and >7 points are considered elevated. The proportion of females and males with elevated anxiety or depression was calculated. The HADS has good psychometric properties in cardiac patients (n=591 patients, 74% male, 63±10 years old) with high internal consistency for anxiety (Cronbach's α=0.86) and depression (Cronbach's α=0.82),[84] strong correlation with other widely used scales such as the Patient Health Questionnaire-9 (r=0.72),[85] and moderate-to-high test-retest reliability (anxiety: r=0.79 to 0.91; depression: r=0.63 to 0.90).[57,84] The MCID for the HADS is set at ≥1.7 points.[84] The HADS was only administered in the Opportunity trial.

Physical activity levels

Physical activity was measured using an ActiGraph GT3X (Pensacola, Florida), a small wearable accelerometer frequently used in research for the assessment of patient MVPA levels in free-living conditions. Patients wore the accelerometer over the right hip on a waist belt during waking hours for seven days, excluding periods when participants engaged in water-related activities (i.e., bathing, swimming). The physical activity analyses were conducted using ActiLife software (v.6.13.4, ActiGraph, LLC). The tri axial GT3X captures movement about the

vertical (y), horizontal (x) and perpendicular (z) axis, creating a composite vector magnitude of the three axes, which is used for the analysis (VM3, $\sqrt{[x^2+y^2+z^2]}$). The ActiLife software converts the raw acceleration data into activity counts and steps. Recommendations on how to process accelerometer data were followed.[86,87] In summary, the data were extracted as 60-sec epochs using a proprietary low-frequency extension filter. Non-wear time was defined as a minimum of 60 minutes of consecutive zero counts per minute (cpm) and was excluded from the analyses. A valid day of physical activity data was defined as ≥10 hours of wear-time and only patients with ≥4 valid days were retained in the analyses.[88] Vector magnitude Sasaki cut-points were chosen to define light (150-2,689 cpm), moderate (2,690-6,166 cpm) and vigorous (≥6,167 cpm) physical activity.[87,89] Weekly minutes of physical activity at each intensity were calculated by multiplying the daily average (min/day) by seven. To minimize reactivity, the first day was removed and the subsequent days were used for the average. These cut-points were developed in a healthy, young population (n=36, sex distribution unknown) and deserve further validation, yet they have been used to assess physical activity levels in AF[90] and CVD populations.[86,91,92] Further, MVPA levels determined using the Sasaki cut-points have been shown to strongly correlate (r=0.91) with Mark cut-points; the latter were developed in patients with CVD, but they may over-estimate the proportion of patients meeting MVPA guidelines.[87] Using the Sasaki cut-points, the proportion of females and males meeting the exercise targets of 200 minutes per week of MVPA from the Canadian Cardiovascular Society AF management guidelines,[3] as well as at least 150 weekly minutes of MVPA as recommended by the Canadian 24-hour movement guidelines for the general adult population,[93] were calculated.

The ActiGraph accelerometer has shown good validity to measure physical activity in healthy and older adults.[94–97] Scarce validity data are available in older adults; studies using

ActiGraph (n=62, 79% females, 75±7 years old, r=0.5 to 0.6) and other triaxial accelerometers (n=29, 60 to 80 years old, r=0.85) suggest a moderate-to-strong correlation with measured physical activity energy expenditure.[96,98] In older adults (n=78, 62% females, 71±5 years old), the ActiGraph GT3X has shown good test-retest reliability (ICC: 0.75 to 0.90) and is able to detect changes over time following an exercise intervention.[99]

Adherence and compliance

Adherence was assessed based on the percentage of exercise sessions attended (i.e., number of sessions attended/sessions offered*100). The proportion of females and males with high adherence (i.e., attending ≥70% of exercise sessions)[100] was calculated. Compliance was assessed by comparing the exercise prescription (e.g., whether HR or power output were within range) with the actual exercise intensity performed by each patient during each session attended.

Sample size

Mean differences between sexes and SDs from studies in patients with AF[32] and heart failure[101] enrolled in CR were used to calculate an effect size and subsequently compute our sample size *a priori* (Power Analysis & Sample Size [PASS] 2019 v.19.0.3). Given the student's timeline, our research experience and previous exercise studies in patients with AF showing greater male than female participation,[32] a 2:1 allocation ratio (2 males: 1 female) was selected for the sample size calculation. Using a SD of 3 mL O_2/kg/min,[8,17,101] a two-sided 0.05 significance level with 80% power (1-β), a total sample size of 108 (36 females and 72 males) was required to compare the mean change in $\dot{V}O_{2peak}$ between sexes using a repeated measures design. To account for an

anticipated 20% dropout rate,[32] a total sample size of 135 was needed (45 females and 90 males) (see Appendix 5.3. for calculations).

Statistical analyses

Statistical analyses were conducted using SPSS for Windows (version 29; IBMCorp, Armonk, New York, United States). All exercise groups (i.e., HIIT, MICT) were collapsed and outcomes were compared between sexes. Descriptive statistics were used to summarize the sample characteristics by sex. Continuous variables are presented as means and standard deviations or medians and 95% confidence interval (CI). Categorical variables are presented as frequencies and percentages. A missing value analysis of the primary measure showed that the data were missing at random. A linear mixed-effects model for repeated measures using the full information maximum likelihood estimation method[102] and unstructured covariate matrix was conducted to examine differences in the measured outcomes following 12 weeks of exercise training with fixed effects of time and sex. Time (baseline versus follow-up), Sex (female versus male), and their interaction 'Time x Sex' were included in the model. All residuals from the linear mixed-effects model were tested for normality using Kolmogorov-Smirnov tests. The residuals of waist circumference, percent body fat, resting HR and diastolic blood pressure were not normally distributed. A two-step approach using the Templeton Method was performed to transform these variables.[103] Because the transformed data showed consistent results with the original data, the latter are reported for descriptive purposes. The same approach was used for secondary outcomes. Chi-square analyses were used to compare the prevalence of patient symptoms, program adherence and compliance, and those achieving MCIDs between sexes. Significance was set at $p<0.05$ (two-sided).

5.5. Results

A total of 34 (31%) females and 77 (69%) males (F: 71±8 vs. M: 68±8 years old, p=0.253) were included in the study. Participant sociodemographic characteristics, medical history and medications are summarized by sex in Table 5.1. The distribution of AF subtypes did not differ by sex (persistent: F: 16 [47%] vs. M: 27 [35%]; permanent: F: 18 [53%], M: 50 [65%]; $\chi 2(1) = 1.430$, p=0.232). A greater proportion of males had coronary artery disease and were prescribed statins, whereas a greater proportion of females than males were prescribed thyroid-related and hormone-replacement medications. Most participants were White, retired, had college or university-level education, were affected by a high-risk waist circumference, hypertension, overweight or obesity and were non-smokers. Obstructive sleep apnea, coronary artery disease and diabetes were the most prevalent comorbidities. Nearly 90% of participants were anti-coagulated and the majority were prescribed β-blockers and anti-hypertensive medications.

Table 5.1. Participant characteristics by sex.

	Females n=34	Males n=77	Total N=110	P values
Sociodemographic and gender-related data, n (%)				
Ethnicity: White	25 (89.3)	54 (91.5)	79 (90.8)	0.342
Work status: Retired	21 (75.0)	41 (69.5)	62 (71.3)	0.756
Education: College or university	22 (78.5)	42 (71.1)	64 (73.6)	0.375
Income: Earning 75K+ per year	9 (37.5)	28 (49.2)	37 (45.1)	0.159
Cardiovascular disease risk factors and previous medical conditions, n (%)				
High-risk waist circumference	16 (53.3)	48 (65.8)	64 (62.1)	0.238
Hypertension	18 (52.9)	44 (57.1)	62 (55.9)	0.681
Elevated body mass index				0.231
Overweight	8 (23.5)	24 (31.2)	32 (28.8)	
Obesity	16 (47.1)	41 (53.2)	57 (51.4)	
Dyslipidemia	6 (17.6)	26 (33.8)	32 (28.8)	0.084
Obstructive sleep apnea	3 (8.8)	14 (18.2)	17 (15.3)	0.207
Coronary artery disease	1 (2.9)	14 (18.2)	15 (13.5)	**0.030**
Diabetes	4 (11.8)	9 (11.7)	13 (11.7)	0.991
Transient ischemic attack or stroke	5 (14.7)	7 (9.1)	12 (10.8)	0.38
Heart failure	2 (5.9)	6 (7.8)	8 (7.2)	0.720
Myocardial infarction	1 (2.9)	5 (6.5)	6 (5.4)	0.446
COPD	0 (0)	5 (6.5)	5 (4.5)	0.128
Valvular disease/ replacement	2 (5.9)	2 (2.6)	4 (3.6)	0.392
Ischemic cardiomyopathy	1 (2.9)	3 (3.9)	4 (3.6)	0.803
Smoker	0 (0)	3 (3.9)	3 (2.7)	0.243
Peripheral vascular disease	1 (2.9)	1 (1.3)	2 (1.8)	0.549
Medications, n (%)				
Anti-coagulant	31 (91.2)	65 (84.4)	96 (86.5)	0.337
β-blocker	19 (55.9)	52 (67.5)	71 (64.0)	0.239
Statin	8 (23.5)	38 (49.4)	46 (41.4)	**0.011**
Calcium channel blocker	11 (32.4)	18 (23.4)	29 (26.1)	0.321
ACE-inhibitor	4 (11.8)	22 (28.6)	26 (23.4)	0.054
Diuretic	8 (23.5)	18 (23.4)	26 (23.4)	0.986
Angiotensin II receptor blocker	9 (26.5)	13 (16.9)	22 (19.8)	0.243
Digoxin	7 (20.6)	8 (10.4)	15 (13.5)	0.147
Thyroid hormone	8 (23.5)	6 (7.8)	14 (12.6)	**0.021**
Anti-platelet	3 (8.8)	11 (14.3)	14 (12.60)	0.424
Oral hypoglycemic	2 (5.9)	8 (10.4)	10 (9.0)	0.445
Nitrate	1 (2.9)	8 (10.4)	9 (8.1)	0.185
Anti-depressant	5 (5.9)	7 (9.1)	9 (8.1)	0.568
Anti-arrhythmic	2 (5.9)	3 (3.9)	5 (4.5)	0.642
Hormone replacement medications	4 (11.8)	0 (0.0)	4 (3.6)	**0.002**
Insulin	1 (2.9)	0 (0)	1 (0.9)	0.131

Data are presented as n (percentage). P<0.05 denotes significance. ACE: Angiotensin-converting enzyme; COPD: Chronic obstructive pulmonary disease.

Primary outcome: peak aerobic power ($\dot{V}O_{2peak}$)

$\dot{V}O_{2peak}$ data were available for 34 females and 75 males at baseline, and 12 females and 31 males at follow-up. Main effects of time, sex and their interaction for the CPET measures are shown in Table 5.2. (see Appendix 5.4. for data reported as medians and 95% CI). A significant main effect of time showed improvements in $\dot{V}O_{2peak}$ (F=7.037, p=0.011), and a significant main effect of sex revealed a lower $\dot{V}O_{2peak}$ in females than males (F=18.658, p<0.001). Improvements in $\dot{V}O_{2peak}$ did not differ between sexes (time-by-sex interaction: F=0.143, p=0.707). Following 12 weeks of exercise training, $\dot{V}O_{2peak}$ increased in females (median [95% CI]: 14.3 [13.3 to 15.1] to 16.9 [12.2 to 21.5] mL O_2/kg/min; +18%) and males (19.0 [17.5 to 20.8] to 21.1 [17.2 to 24.0] mL O_2/kg/min; +11%) (see Figure 5.1.). After adjusting for FFM, a significant main effect of time showed improvements in $\dot{V}O_{2peak}$ (F=7.444, p=0.010), yet no sex differences remained (F=2.714, p=0.103, see Figure 5.1.).

A per protocol analysis among patients who attended ≥70% of the sessions showed similar effects of time (F=6.595, p=0.014) and sex (F=11.344, p=0.001), without a time-by-sex interaction for $\dot{V}O_{2peak}$ differences in mL O_2/kg/min (F=0.056, p=0.813). Similarly, when including only patients with both baseline and follow-up $\dot{V}O_{2peak}$ values (n=43), significant effects of time (F=6.353, p=0.016) and sex (F=5.805, p=0.020) were revealed, without an interaction (F=0.052, p=0.821). Among those who performed a follow-up CPET, 42% of females and 47% of males achieved at least a 1.75 mL/kg/min $\dot{V}O_{2peak}$ improvement (χ2(2)=1.372, p=0.503). At baseline, 71% of females and 75% of males (χ2(3)=6.290, p=0.093) had a $\dot{V}O_{2peak}$ within the "very poor" category as per ACSM's classification for the general population. These proportions were reduced to 42% in females and 60% in males following 12 weeks of exercise training (χ2(4)=7.609, p=0.107).

Table 5.2. Baseline and follow-up data of continuous outcomes in patients with persistent and permanent atrial fibrillation.

Variables	Females		Males		Time effect	Sex effect	time*sex
	Baseline	Follow-up	Baseline	Follow-up			
Peak aerobic power							
$\dot{V}O_{2peak}$ (mL O_2/kg/min)	14.9 ± 3.5 (n=34)	17.2 ± 5.3 (n=12)	19.4 ± 5.0 (n=75)	20.8 ± 4.9 (n=31)	**0.011**	**<0.001**	0.707
$\dot{V}O_{2peak}$ (mL O_2/kg of FFM/min)	24.5 ± 5.9 (n=30)	28.8 ± 7.7 (n=10)	27.3 ± 6.71 (n=71)	28.9 ± 6.4 (n=26)	**0.010**	0.103	0.696
$\dot{V}O_{2peak}$ (L O_2/min)	1.17 ± 0.37 (n=34)	1.47 ± 0.51 (n=12)	1.83 ± 0.47 (n=75)	1.98 ± 0.46 (n=31)	**0.010**	**<0.001**	0.590
Peak power output (Watts)	112.6 ± 33.3 (n=34)	142.4 ± 57.8 (n=17)	151.3 ± 37.9 (n=76)	179.4 ± 38.2 (n=33)	**<0.001**	**<0.001**	0.909
AF-specific quality of life (AFSS), points	n=34	n=30	n=75	n=62			
Global wellbeing (1-10)	7.4 ± 2.0	8.0 ± 1.5	7.3 ± 1.9	7. 7 ± 1.6	**0.006**	0.669	0.452
Frequency of AF (1-10)	2.4 ± 2.4	2.7 ± 2.8	1.5 ± 1.5	1.6 ± 1.4	0.672	**0.002**	0.768
Duration of AF (1-10)	2.6 ± 2.6	3.22 ± 3.08	1.79 ± 2.01	1.88 ± 1.98	0.196	**0.005**	0.224
Severity of AF (1-10)	4.1 ± 2.6	4.1 ± 2.7	3.5 ± 2.3	2.9 ± 2.3	0.089	**0.041**	0.084
Visits to the emergency department	0.6 ± 1.2	0.5 ± 1.2	0.4 ± 0.9	0.4 ± 1.0	0.429	0.405	0.522
Hospitalizations	0.1 ± 0.4	0.1 ± 0.3	0.2 ± 0.6	0.1 ± 0.4	0.239	0.692	0.576
Specialist visits	1.5 ± 1.1	1.3 ± 1.5	1.3 ± 1.4	1.2 ± 1. 5	0.103	0.506	0.770
Total burden (0-30)	21.3 ± 5.3	19.4 ± 7.1	22.2 ± 3.3	21.2 ± 3.5	**0.004**	0.154	0.413
Symptom score (0-35)	9.2 ± 6.4	8.2 ± 6.3	8.1 ± 5.6	6.6 ± 4.9	**0.002**	0.144	0.271
General quality of life (SF-36), points	n=34	n=30	n=75	n=63			
Physical functioning	43.2 ± 9.2	44.8 ± 8.6	43.7 ± 9.7	46.1± 9.9	**0.007**	0.553	0.294
Role limitations due to physical problems	41.7 ± 11.7	44.5 ± 11.1	43.5 ± 11.6	44.8 ± 11.3	0.229	0.670	0.619
Bodily pain	36.8 ± 7.4	36.5 ± 6.4	38.4 ± 7.2	37.0 ± 7.6	0.335	0.462	0.459
General health	46.6 ± 9.6	47.6 ± 8.4	43.1 ± 9.0	44.4 ± 9.7	0.273	0.108	0.333
Vitality	46.7 ± 10.0	47.0 ± 9.8	46.5 ± 9.3	48.4 ± 7.8	0.215	0.671	0.086

Social functioning	49.0 ± 10.4	51.9 ± 9.1	49.7 ± 9.7	50.3 ± 9.1	0.066	0.927	0.278
Role limitations due to emotional issues	50.2 ± 10.4	52.3 ± 7.7	49.2 ± 10.6	50.9 ± 9.2	0.152	0.588	0.855
Mental health	51.4 ± 7.8	52.4 ± 7.5	51.7 ± 8.1	52.9 ± 8.1	0.221	0.629	0.570
Physical component summary	38.6 ± 8.5	39.9 ± 7.5	39.3 ± 8.0	40.1 ± 7.9	0.280	0.874	0.678
Mental component summary	53.8 ± 9.5	55.2 ± 7.2	53.1 ± 9.8	54.4 ± 8.6	0.150	0.876	0.588
Functional capacity	n=33	n=29	n=70	n=59			
6-minute walk test distance (m)	493 ± 88	515 ± 89	528 ± 112	544 ± 132	**0.001**	0.159	0.466
Hemodynamic and anthropometric data	n=30 to 34	n=25 to 3	n=73 to 77	n=56 to 64			
Resting heart rate (bpm)	78 ± 13	74 ± 12	70 ± 12	67 ± 12	**0.025**	**0.001**	0.524
Resting systolic BP (mmHg)	124 ± 17	123 ± 16	126 ± 16	125 ± 17	0.666	0.535	0.844
Resting diastolic BP (mmHg)	78 ± 11	77 ± 9	79 ± 9	78 ± 10	0.280	0.665	0.496
Body mass (kg)	80.1 ± 22.6	79.5 ± 24.1	95.9 ± 17.4	95.3 ± 18.2	0.081	**<0.001**	0.772
Body mass index (kg/m^2)	30.1 ± 7.3	29.7 ± 7.8	30.4 ± 5.1	30.2 ± 5.5	0.067	0.741	0.673
Waist circumference (cm)	93.1 ± 16.2	91.3 ± 16.4	107.1 ± 12.5	105.1 ± 12.5	**0.037**	**<0.001**	0.398
Body fat (%)	37.2 ± 8.1	35.6 ± 10.7	27.9 ± 7.0	28.2 ± 6.9	0.126	**<0.001**	0.209
Fat mass (kg)	29.8 ± 12.2	28.7 ± 14.8	27.5 ± 10.9	27.9 ± 10.6	0.269	0.360	0.540
Fat-free mass (%)	62.8 ± 8.1	64.4 ± 10.7	72.1 ± 7.0	71.8 ± 6.9	0.722	**<0.001**	0.908
Fat-free mass (kg)	47.6 ± 8.2	47.4 ± 7.2	68.2 ± 9.1	68.2 ± 9.6	0.126	**<0.001**	0.209
Anxiety and depression	n=20	n=23	n=38	n=44			
Anxiety (points)	5.5 ± 3.2	4.5 ± 2.7	4.6 ± 3.4	4.3 ± 3.4	**0.018**	0.425	0.734
Depression (points)	4.2 ± 4.2	2.3 ± 2.2	4.5 ± 3.2	3.2 ± 2.6	**<0.001**	0.372	0.808
Device-measured physical activity	n=33	n=29	n=69	n=60			
Light physical activity (min/week)	2,310 ± 660	2,181 ± 561	1,927 ± 574	2,006 ± 643	0.659	**0.016**	**0.034**
Moderate physical activity (min/week)	139 ± 124	161 ± 119	161 ± 157	188 ± 164	0.329	0.605	0.621
Vigorous physical activity (min/week)	4.4 ± 11.1	2.9 ± 6.6	3.9 ± 10.9	3.6 ± 8.3	0.531	0.948	0.760
MVPA (min/week)	144 ± 133	164 ± 122	165 ± 162	191 ± 166	0.364	0.625	0.635
Step counts per week	31,728 ± 18,245	35,007 ± 17,321	31,002 ± 18,209	35,029 ± 19,123	0.055	0.816	0.784

Values are presented as means ± standard deviations. P<0.05 denotes significance. AF: Atrial fibrillation; BP: Blood pressure; FFM: Fat-free mass; MVPA: Moderate- to vigorous-intensity physical activity; $\dot{V}O_{2peak}$: Peak aerobic power.

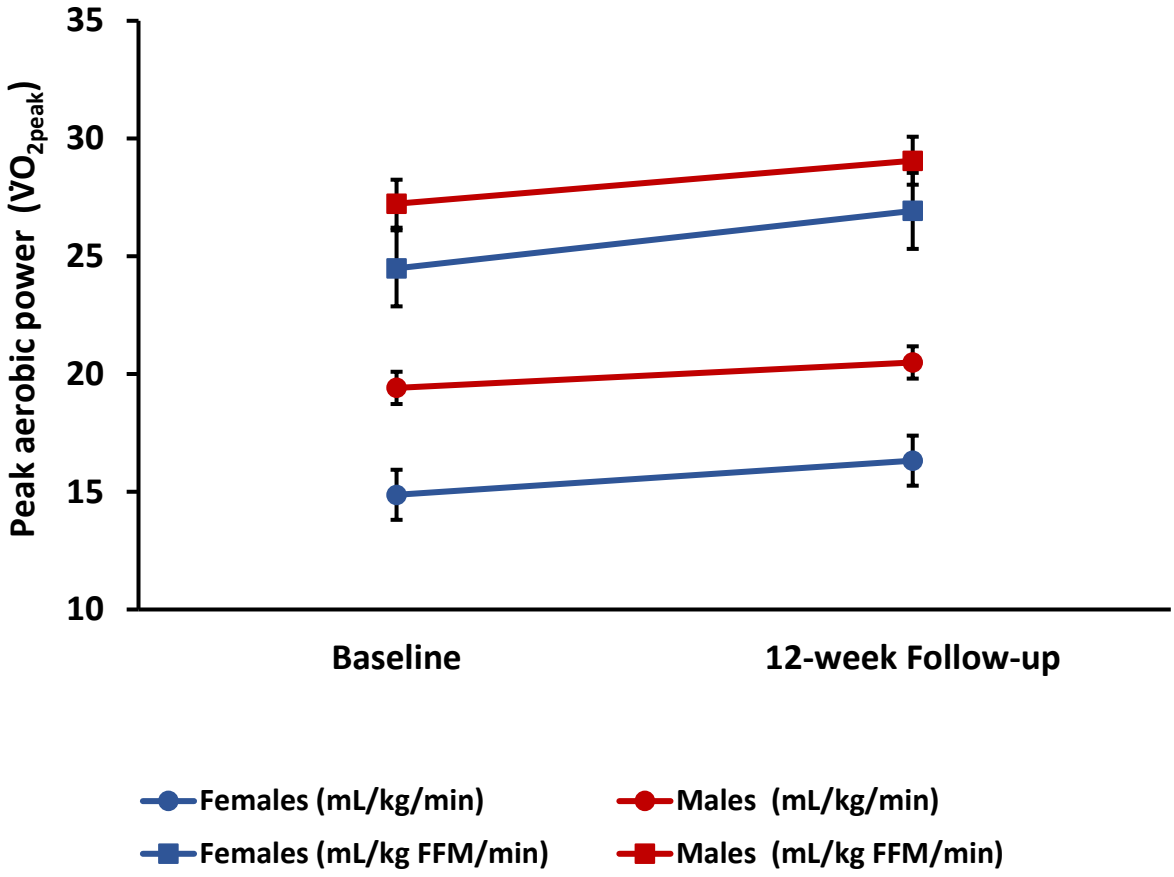


Figure 5.1. Changes in $\dot{V}O_{2peak}$ adjusted by body mass and fat-free mass in females and males with persistent and permanent atrial fibrillation following 12 weeks of aerobic exercise training. Data presented as estimated marginal means and standard errors from the mixed model. FFM: Fat-free mass.

Additional physical and mental health outcomes

Main effects of time, sex and their interaction for continuous outcomes are shown in Table 5.2.

AF symptoms and QoL. The prevalence of patient AF symptoms as measured by the CCS-SAF was not significantly different between sexes at baseline or follow-up (Figure 5.2.). Several symptoms were highly prevalent among participants. Palpitations were reported by 21 (62%) and 15 (52%) females, and 33 (43%) and 21 (33%) males at baseline (χ2(1)=3.163, p=0.075) and

follow-up (χ2(1)=2.820, p=0.093), respectively. Fatigue was reported by 20 (59%) and 15 (52%) females, and 50 (66%) and 31 (49%) males at baseline (χ2(1)=0.493, p=0.483) and follow-up (χ2(1)=0.050, p=0.822), respectively. Dyspnea was reported by 19 (56%) and 18 (62%) females, and 41 (54%) and 28 (44%) males at baseline (χ2(1)=0.035, p=0.851) and follow-up (χ2(1)=2.467, p=0.116), respectively. At both time points, more than 70% of patients associated their symptoms with AF, and approximately 70% of females when compared to 55% of males reported that their AF symptoms limited their daily activities (χ2(1)=2.153, p=0.142).

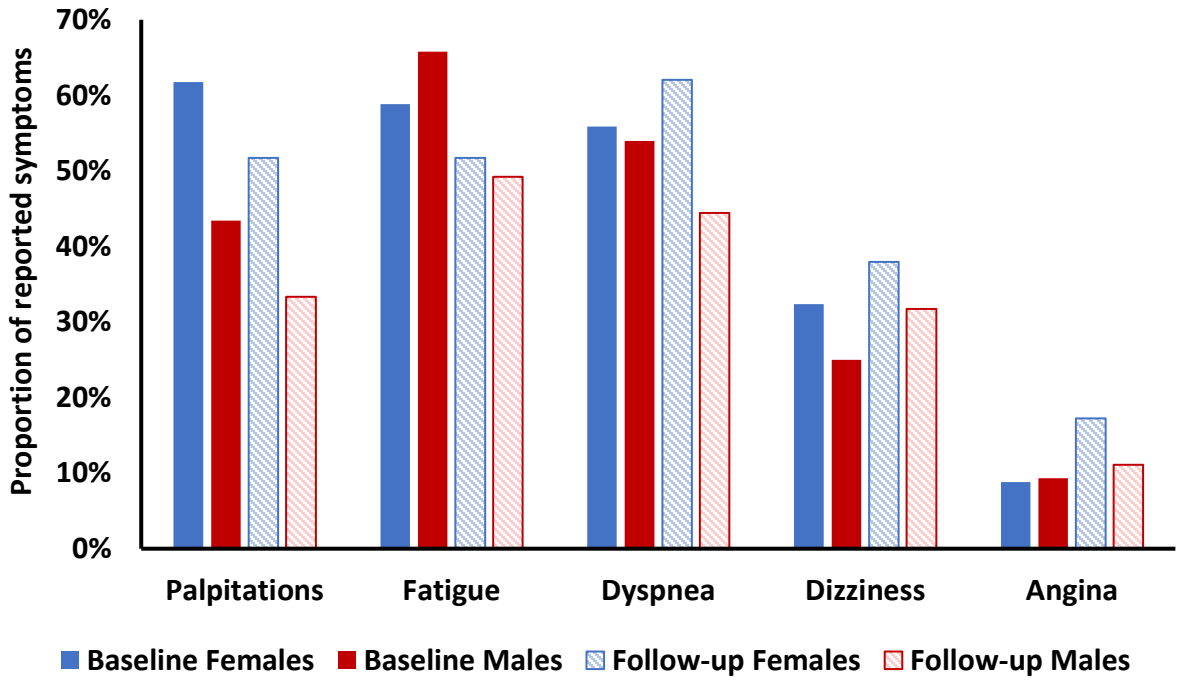


Figure 5.2. Proportion of females and males with persistent and permanent atrial fibrillation reporting symptoms at baseline and following a 12-week exercise program.

Main effects of time, sex and their interaction for the AF-specific and general QoL of patients are shown in Table 5.2. Significant main effects of time showed an increase in global well-being (mean ± SD: F: 7.4±2.0 to 8.0±1.5 points; M: 7.3±1.9 to 7. 7±1.6 points; F=7.759, p=0.006) and reductions in self-reported total AF burden (F: 21.3±5.3 to 19.4±7.1 points; M: 22.2±3.3 to 21.2±3.5 points; F=8.702, p=0.004) and symptom score (F: 9.2±6.4 to 8.2±6.3 points; 8.1±5.6 to 6.6±4.9 points; F=9.968, p=0.002). Significant main effects of sex revealed greater self-reported frequency (F=10.309, p=0.002), duration (F=8.250, p=0.005) and severity (F=4.261, p=0.041) of AF in females than males. Only the physical function subscale of the SF-36 improved over time (F: 43.2±9.2 points to 44.8±8.6 points; M: 43.7±9.7 to 46.1± 9.9 points; F=7.605, p=0.007); no sex differences were noted in general QoL. There were no time-by-sex interactions in AF-specific or general QoL following 12 weeks of exercise training. Following exercise training, 7 (24%) females and 21 (35%) males achieved a 3-point reduction in the AFSS symptom score (χ2(1)=1.070, p=0.301). The 5-point MCID for the PCS (χ2(2)=0.209, p=0.901) and MCS (χ2(2)=2.649, p=0.266) was achieved by 21% and 14% of females, and 25% and 28% of males, respectively.

Functional capacity. Significant main effects of time showed an increase in the 6MWT distance following exercise training (F: 493±88 to 515±89 metres; M: 528±112 to 544 ± 132 metres; F=10.834, p=0.001), without significant sex differences or interactions (see Table 5.2). Following exercise training, 14% of females and 26% of males achieved the MCID of 54 metres (χ2(2)=2.058, p=0.357). The proportion of females and males with a low functional capacity (<450 metres) was 24% and 21% at baseline (χ2(1)=0.527, p=0.468), respectively, and 21% and 12% at 12-week follow-up (χ2(1)=1.059, p=0.303).

Hemodynamic and anthropometric measures. Main effects of time, sex and their interaction for hemodynamic and anthropometric data are shown in Table 5.2. There were reductions in resting HR (F=5.217, p=0.025) and waist circumference (F=4.497, p=0.037) over time. Significant main effects of sex revealed a higher resting HR (F=10.688, p=0.001), lower body mass (F=16.332, p<0.001), waist circumference (F=22.954, p<0.001) and percent fat-free mass (F=30.609, p<0.001), and higher percent body fat (F=30.609, p<0.001) in females than males. No significant time-by-sex interactions were observed. The proportion of females and males with a high-risk waist circumference (F: ≥88 cm, M: ≥102 cm) was 53% and 66% at baseline (χ2(1)=1.394, p=0.238), respectively, and 52% and 61% at follow-up (χ2(1)=0.643, p=0.423).

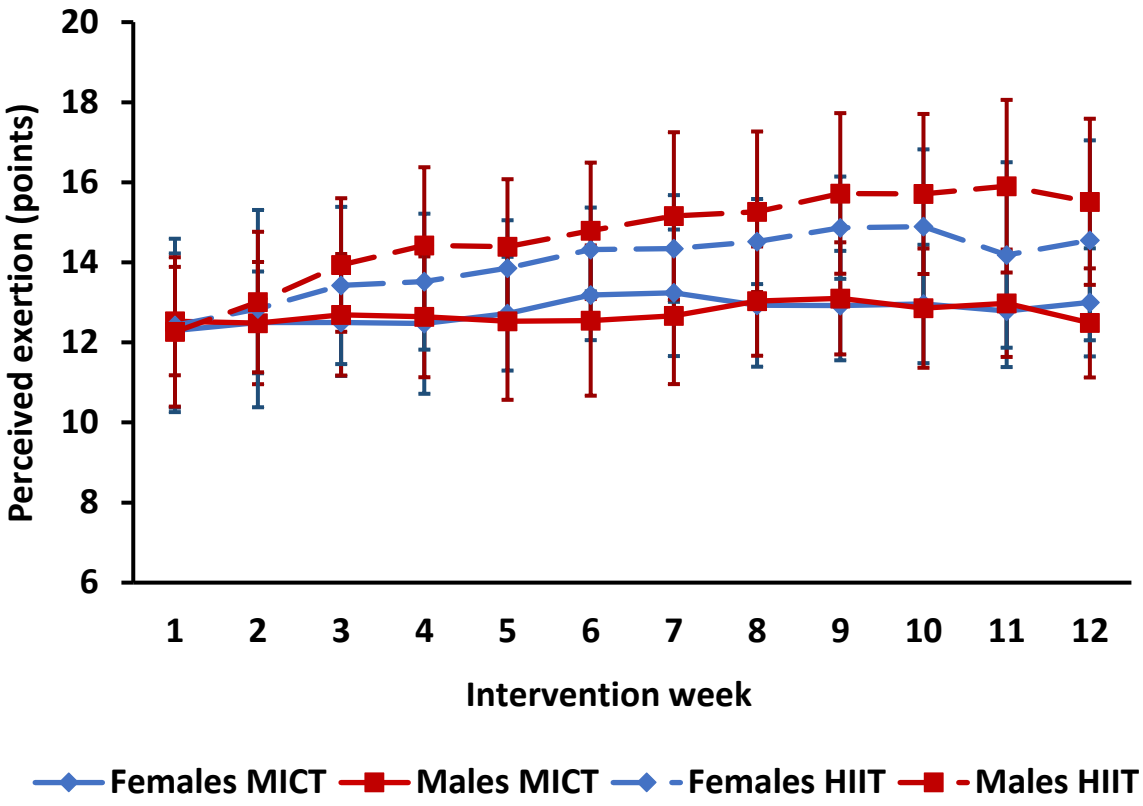
Anxiety and depression. HADS data were available for 20 females and 38 males at baseline, and 23 females and 44 males at follow-up. Anxiety (F=5.998, p<0.001) and depression (F=14.889, p<0.001) improved over time following exercise training. No sex differences or significant time-by-sex interactions were noted for these mental health outcomes (see Table 5.2.). A smaller proportion of females than males achieved the 1.7-point MCID for depression (F: 2 [13%] vs. M: 12 [40%]; χ2(2)=6.520, p=0.038); no sex differences were noted for anxiety (χ2(2)=0.247, p=0.884). At baseline, elevated anxiety and depression (> 7 points) were reported by 3 (16%) and 3 (16%) females, and 6 (19%) and 4 (13%) males, respectively (χ2(1)=0.101, p=0.750; χ2(1)=0.082, p=0.775). At follow-up, elevated anxiety and depression were reported by 3 (13%) and 1 (4%) females; and 6 (14%) and 3 (7%) males, respectively (χ2(1)=0.005, p=0.946; χ2(1)=0.164, p=0.685).

Physical activity levels. A significant time-by-sex interaction (F=4.626, p=0.034) was found such that following exercise training light physical activity levels decreased in females (2,310±660 to 2,181±561 minutes per week) and increased in males with AF (1,927±574 to

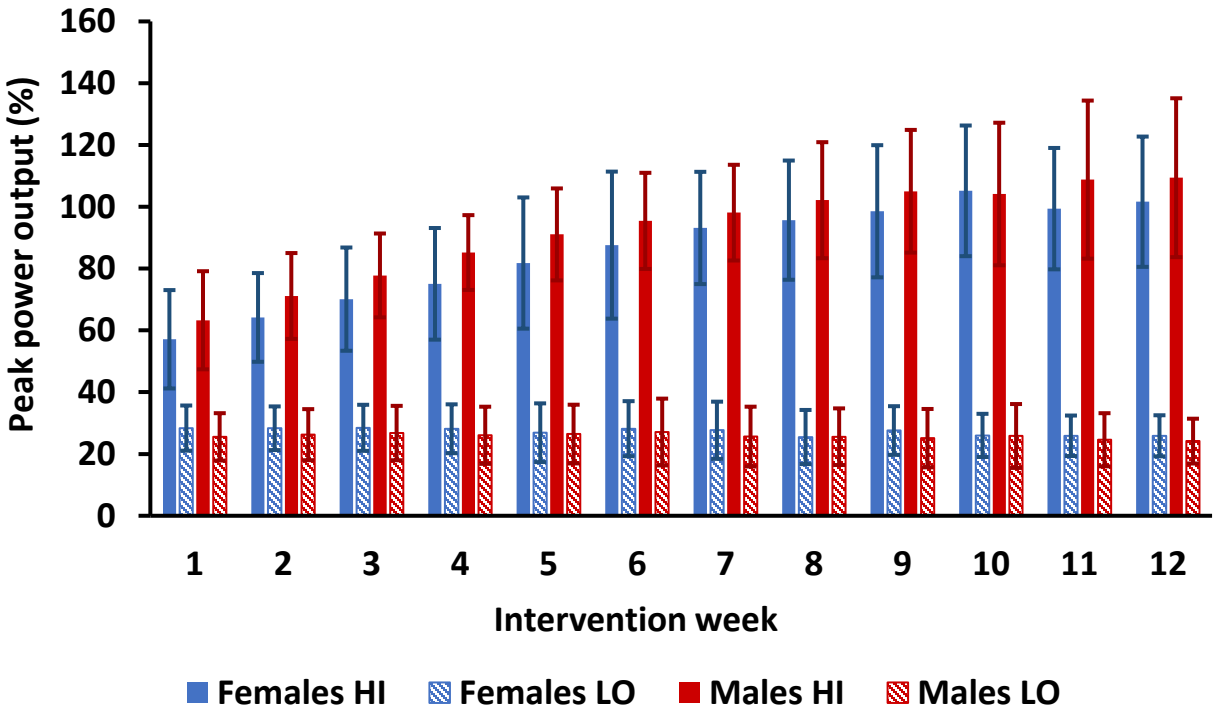
2,006±643 minutes per week). No sex differences were found in the proportion of females and males meeting the physical activity guidelines at any time point. At baseline (χ2(1)=0.321, p=0.571) and 12-week follow-up (χ2(1)=0.200, p=0.655), 11 (33%) and 15 (52%) females, and 27 (39%) and 28 (47%) males, respectively, met at least 150 minutes per week of MVPA.

Dropouts, adherence, and compliance. Of the 34 females and 77 males included in the study, four (12%) females and 13 (17%) males dropped out of the exercise program (χ2(1)=0.476, p=0.490). A total of 18 (53%) females and 18 (48%) males participated in HIIT; whereas 16 (47%) females and 40 (52%) males participated in MICT (χ2(1)=0.226, p=0.635). Program attendance did not differ by sex (F: 80±22%, M: 83±21% of sessions attended, p=0.437); 26 (79%) females and 60 (83%) males attended at least 70% of sessions and were classified as having high adherence (χ2(1)=0.172, p=0.678). Figure 5.3. summarizes the RPE, percent PPO and percent HR_{peak} at which participants exercised by sex during the 12-week program. A total of 67% of females and 73% of males were considered compliant with the exercise prescription (χ2(1)=0.387, p=0.534). Among females, high adherence was achieved by 77% of participants in HIIT and 81% in MICT (χ2(1)=0.113, p=0.737). A total of 9 (53%) females in HIIT and 13 (81%) females in MICT were classified as complying with the exercise prescription (χ2(1)=2.972, p=0.085). Among males, high adherence was achieved by 78% of participants in HIIT and 87% in MICT (χ2(1)=0.945, p=0.331). A total of 25 (69%) males in HIIT and 28 (76%) males in MICT were classified as complying with the exercise prescription (χ2(1)=0.356, p=0.551).

A)


Perceived exertion (points)
20
18
16
14
12
10
8
6
1
2
3
4
5
6
7
8
9
10
11
12
Intervention week
Females MICT
Males MICT
Females HIIT
Males HIIT

B)


Peak power output (%)
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
12
Intervention week
Females HI
Females LO
Males HI
Males LO

C)

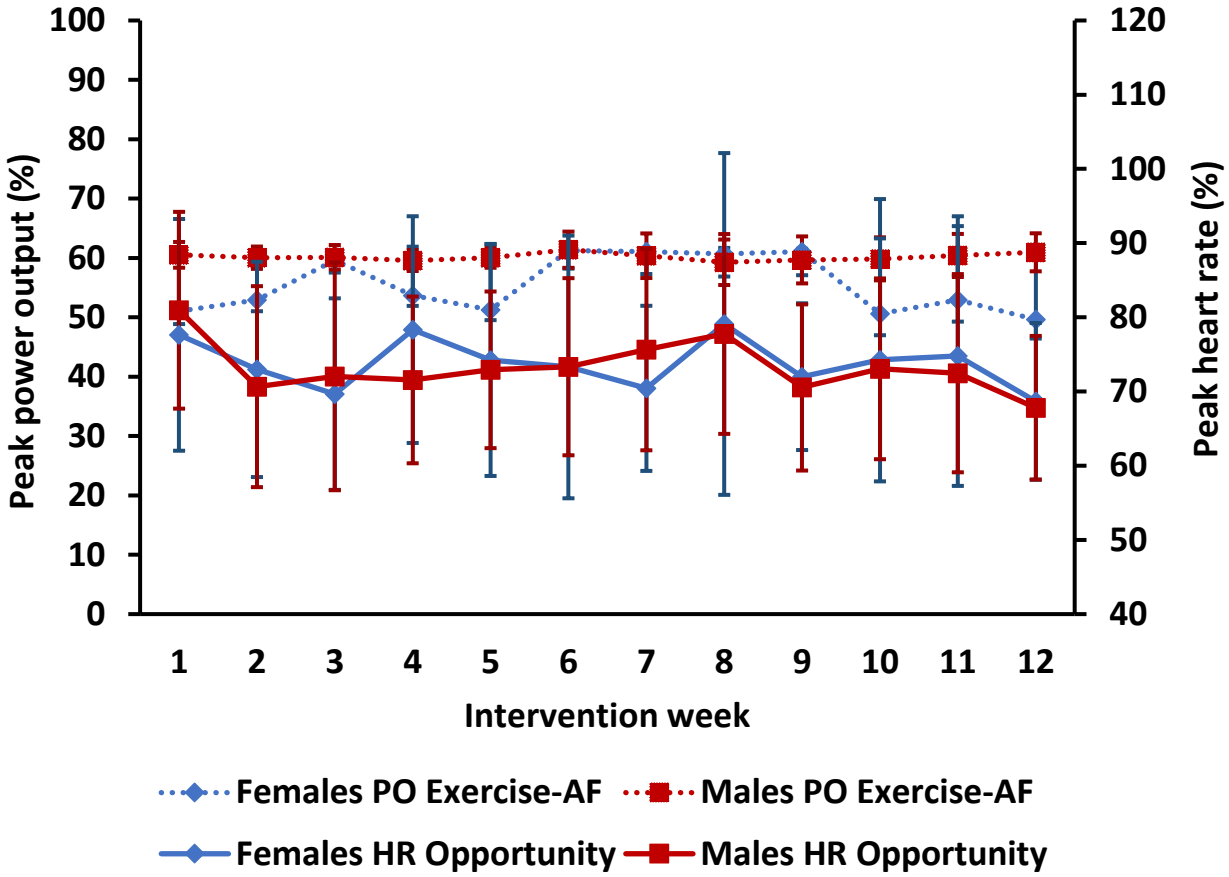


Figure 5.3. Exercise training responses in patients with persistent and permanent atrial fibrillation by sex. Values are plotted as means and standard deviations. Data include: (A) ratings of perceived exertion, (B) percentage of peak power output during high-intensity interval training; and, (C) percentage of peak power output (Exercise-AF trial) and percentage of peak heart rate (Opportunity trial) during moderate- to vigorous-intensity continuous training, from intervention week 1 to 12. HI: High-intensity work bout; HIIT: High-intensity interval training; HR: Heart rate; LO: Active recovery bout; MICT: Moderate- to vigorous-intensity continuous training; PO: Power output.

5.6. Discussion

This novel study compared differences in physical and mental health outcomes over time between females and males with persistent and permanent AF who participated in 12 weeks of exercise training. Contrary to our hypothesis, no differences were observed in $\dot{V}O_{2peak}$ over time between sexes. Twelve weeks of exercise training led to $\dot{V}O_{2peak}$ improvements in females (median change: +2.6 mL O_2/kg/min; +18%) and males (median change: +2.1 mL O_2/kg/min; +11%); these changes surpass the suggested clinical threshold of 1.75 mL O_2/kg/min.[56,57] Weekly minutes of light physical activity decreased in females (median change: -55 minutes per week) and increased in males (+193 minutes per week) following the exercise programs.

Primary outcome: peak aerobic power ($\dot{V}O_{2peak}$)

$\dot{V}O_{2peak}$ is an indicator of the risk for AF recurrence[10] and is considered a vital sign,[55] thus, it is often used to test the efficacy of exercise interventions. In patients with non-permanent AF affected by overweight/obesity (n=308, ~50% female), every 1 metabolic equivalent (MET; 1 MET=$\dot{V}O_2$ of 3.5 mL O_2/kg/min) increase in $\dot{V}O_{2peak}$ has been shown to reduce AF recurrence by 9% after adjustment for changes in CVD risk factors.[10] Scarce data (n=292 patients with AF, 24% female) suggests a 17% lower risk of CVD hospitalization or all-cause mortality with every 1 MET increase following CR participation.[11] In our study, 42% of females and 47% of males reached a clinically important $\dot{V}O_{2peak}$ change (≥1.75 mL O_2/kg/min or 0.5 METs)[56] which could translate into a 5 to 10% reduction in AF recurrence and mortality. Our mean baseline $\dot{V}O_{2peak}$ (F: 14.9±3.5, M: 19.4±5.0 mL O_2/kg/min) and change values (F: +1.3±2.0; M: +1.1±3.2 mL O_2/kg/min) were lower than those reported in the CopenHeartRFA trial, the only CR program in AF whose authors segregate outcomes by sex (n=59 females, 151 males).[32] Twelve weeks of triweekly combined aerobic and resistance training led to a $\dot{V}O_{2peak}$ increase of 1.7 mL

O_2/kg/min in females (baseline: 20.0±5.2 mL O_2/kg/min) and 2.9 mL O_2/kg/min in males (baseline: 27.7±9.4 mL O_2/kg/min), respectively.[32] Differences in participant (e.g., in CopenHeartRFA patients had undergone an ablation and were younger [~61 years]) and program (e.g., CopenHeartRFA offered 3 weekly exercise sessions and a choice to exercise in the community) characteristics may have affected the response to the exercise programs. Although our findings are positive and support the efficacy of exercise to improve $\dot{V}O_{2peak}$ in females and males with AF, a greater exercise volume, longer intervention, or additional lifestyle-based strategies (e.g., resistance training, behaviour coaching) may benefit the 58% of females and 53% of males who did not reach the 1.75 mL O_2/kg/min target, and those (F: 42%, M: 60%) who continued to have a *very poor* cardiorespiratory fitness at follow-up.

Main effects of sex revealed that females had a 4.35 mL O_2/kg/min (estimated marginal mean from the model) smaller $\dot{V}O_{2peak}$ than males, this aligns with previous literature in patients with AF and CVD (3.8 to 7.5 mL O_2/kg/min lower $\dot{V}O_{2peak}$ in females).[32,104,105] Given the association of $\dot{V}O_{2peak}$ with AF recurrence and mortality, this sex difference appears clinically relevant and may contribute to the worse prognosis in females than males, yet this deserves further examination. When adjusted by FFM, a 2.4 mL O_2/kg/min difference remained, but it was no longer significant. Thus, differences in body composition between females and males are mostly responsible for sex differences in $\dot{V}O_{2peak}$. In addition, the higher HR in females than males may limit the preload, stroke volume and subsequent $\dot{V}O_{2peak.}$ The proportion of patients in the "*very poor*" cardiorespiratory fitness category did not differ by sex and decreased by 29% in females and 15% in males following 12 weeks of exercise training. These ACSM categories have sex-specific cut-offs, yet they are based on healthy adults.[59]

Sensitivity analyses of the primary outcome in those who attended at least 70% of the prescribed exercise sessions (n=26 [79%] females, 60 [82%] males) led to similar findings. In accordance, adding to the linear mixed-effects model the intervention type (i.e., HIIT or MICT) as a covariate did not alter the findings and revealed significant effects of time (F=5.239, p=0.027) and sex (F=7.592, p=0.007).

Secondary outcomes

Several patient measures of AF-specific and general QoL, functional capacity, and CVD risk factors such as resting HR, waist circumference, anxiety and depression improved following exercise training. Females reported greater AF frequency, duration and severity; had a higher resting HR and percent body fat, and lower body mass, FFM and waist circumference than males. A time-by-sex interaction was noted, such that following exercise training, light physical activity increased in males, but not females.

AF symptoms and AF-specific and general QoL. The constant fibrillation of the atria in those with persistent and permanent AF leads to symptoms of palpitations, fatigue and dyspnea in 55 to 73% of patients.[20] In our study, most patients reported several AF symptoms based on the CCS-SAF. Significance was not achieved, but 19% more females than males reported palpitations at baseline and 12 weeks (p=0.075 and p=0.093, respectively). A 20% sex difference in palpitations reporting has been previously found in patients with permanent AF.[106] In both sexes, the prevalence of palpitations (F: -10%, M: -10%) and fatigue (F: -7%, M: -17%) decreased following exercise training, providing additional evidence of the benefits of exercise.

Greater AFSS scores have been associated with a higher risk for CVD morbidity and mortality, including hospitalizations for heart failure.[107] Our patients were moderately symptomatic (F: 9.2±6.4, M: 8.1±5.6 points), consistent with findings from the RACE-II study

(N=558 patients with permanent AF, ~35% females, 7.8±6.3 points).[107] Few exercise studies have used AF-specific QoL measures, making comparing studies difficult. The mean global well-being (0-10 range) was 7.4 points in females and 7.3 points in males, demonstrating good self-perceived health, and improved on average by 0.5 points following exercise training. Consistent with previous AF literature,[31,34,35] females self-reported greater AF frequency, duration and severity; this sex difference was less than 2 points and may not be clinically significant. Self-reported total AF burden and symptom scores improved over time, without sex effects or a time-by-sex interaction. These data contrast with a previous retrospective study which, albeit with a small sample size (n=24 patients with persistent and permanent AF), did not reveal improvements in AF burden following CR (21.3±4.8 to 20.7±5.7 points, p=0.345).[108]

The improvements In patient well-being, symptom prevalence and severity over time are mechanistically plausible given the increase in $\dot{V}O_{2peak}$ and functional capacity observed in this study, which may have: (i) increased the stroke volume, in turn lowering patient's resting HR and symptoms of palpitations; (ii) diminished the fatigue that patients experience during activities of daily living; and, (iii) improved their global well-being. Notwithstanding, following the intervention, more than two thirds of females and more than half of males reported that symptoms negatively impacted their daily activities. Further, less than one third of patients reached the MCID for the 6MWT distance, a measure of functional capacity. Patients with AF are often elderly (median age: 75 years)[109] and frail (~54% frail, 46% pre-frail).[110] Future exercise trials may benefit from adjunct exercise strategies that meet the needs of AF patients (e.g., mobility, stretching and resistance training that translate into improved functionality in activities of daily life).

The typical MCS and PCS range for the general population has been established at 40 to 60 points.[111] Our baseline MCS (F: 54±10; M: 53±10 points) scores align with those of the RACE-II study in patients with permanent AF (F: 54±9 M: 53±9).[106] We did not find sex differences in PCS scores (F: 39±9; M: 39±8 points), whilst the RACE-II study reported lower scores in females (F: 39±10 M: 46±8, $p<0.001$).[106] The latter aligns with normative SF-36 values in patients with other CVDs (e.g., myocardial infarction, heart failure) which have shown a 4-point lower PCS and MCS score in females than males.[111] The close to normal general QoL values in females and males in this study may explain the small improvements following exercise training (i.e., only physical function improved over time).

Additional secondary outcomes. Exercise training led to statistically significant reductions in cardiometabolic markers and CVD risk factors without a time by sex interaction, including resting HR (~4 bpm), waist circumference (~2 cm) anxiety (~1 point) and depression (~1.5 point). Contrary to other studies,[8,13–15,24,26] no reduction in body mass and BMI was observed over time ($p=0.081$, $p=0.067$, respectively) among our patients. The sex differences observed in these CVD risk factors, including a higher resting HR and percent body fat, and lower body mass, FFM and waist circumference in females than males align with previous literature in AF and CVD populations.[31,36,104] The scarce studies on mental health in AF suggest a greater risk for anxiety and depression in females than males.[37] Few participants reported on anxiety and depression since funding for this measure became available later in the Opportunity trial. The small sample size, and the low prevalence of elevated anxiety and depression, may have precluded identifying sex differences in the linear mixed-effects model. We did, however, observe that 27% fewer females than males reached the MCID for depression. Future studies

powered to examine sex differences in the effects of exercise training on CVD risk factors, including anxiety and depression, are needed before establishing clear conclusions.

Finally, the time-by-sex interaction in physical activity revealed an increase in light physical activity in males, and a decrease in females. The mean weekly minutes of light physical activity remained higher in females (2,181±561 minutes) than males (2,006±643 minutes) at 12-week follow-up. The opposite was observed for MVPA, suggesting that females may prefer to engage in activities of lower intensities. Indeed, our previous work has shown that more females than males with AF lack confidence in performing physical activity of moderate intensity.[112] In contrast with previous studies,[12,17] no significant improvements were noted in MVPA levels. This could have been affected using cycling as the main exercise modality, which may have encouraged participants to start to more regularly engage in this type of physical activity which cannot be captured with the ActiGraph accelerometer. Nevertheless, we need additional strategies to enhance physical activity participation, as nearly 50% of females and males with AF were not meeting at least 150 minutes per week of MVPA, despite strong evidence supporting the health benefits of being regularly active.[113]

Dropouts, adherence, and compliance. Reasons for dropout in females included: health issues (n=1), fall at home (n=1) and stopped attending exercise sessions (n=1). Males dropped out due to: knee discomfort or injury (n=3), neurocognitive issues (n=1), coronary artery bypass graft (n=1), other health issues (n=4), deceased (n=1), stopped attending classes (n=2) and missing the 12-week follow-up due to covid symptoms (n=1). Approximately 30% of patients with AF are hospitalized at least once a year;[114] thus, we expected that health issues would preclude several participants from finishing the 12-week program. We did not find sex differences in adherence (F: 80% vs. M: 83%), compliance with the exercise prescription (F: 67% vs. M: 73%) or dropout

rates (F: 12% vs. M: 17%). In contrast, previous CVD literature has shown lower or similar adherence and compliance,[45,115,116] and higher or similar dropout rates[116,117] in females than males attending exercise-based CR. The high adherence (~80% of participants) and compliance (~70% of participants) in both sexes suggest that patients with this disabling cardiac arrhythmia and multiple co-morbidities[118] can engage in HIIT and MICT. The CopenHeartRFA trial reported a lower adherence, with a 40% and 47% adherence to CR in females and males with non-permanent AF, respectively. In the present study, sensitivity analyses comparing the adherence and compliance in each sex by intervention revealed a near significant difference ($p=0.085$), such that 53% of females complied with the prescription in HIIT when compared to 81% in MICT. Further examination on the feasibility of HIIT for females with AF is warranted.

The physical and mental health improvements following 12 weeks of HIIT and MICT, and the high adherence observed in the study, provide additional evidence of the promising impact that a supervised, exercise-based CR could have as an adjunct therapy in females and males with AF. The guidelines for the clinical management of patients with AF have moved in the right direction by incorporating specific exercise targets, but exercise-based CR is not routinely provided as an adjunct therapy.[119]

Strengths and limitations

This study has several strengths and limitations to consider. This was a comprehensive sex-based examination that: (i) measured a wide range of physical and mental health outcomes and health behaviours, including patient-reported (e.g., AF-specific and General QoL) and device-measured (e.g., $\dot{V}O_{2peak}$ and MVPA) outcomes; and (ii) implemented several exercise paradigms (i.e., HIIT, MICT). Data prospectively collected from two RCTs were included, allowing us to

maximize the sample size. We did not reach our *a priori* sample size calculation (45 females and 90 males), as only 34 females and 77 males were included in the study. Yet, our dropout rate was lower (F: 12% and M: 17%) than anticipated (20%), and our sample of females was larger than most exercise trials in adults with AF to date.[46] Nevertheless, the female representation in our trial was 16% lower than the female distribution in AF prevalence data worldwide.[120] The clinical notes of the included patients did not appear to discern between persistent and longstanding persistent AF classifications. Follow-up $\dot{V}O_{2peak}$ data was only available from approximately half-way through the Opportunity trial and for the Exercise-AF trial, reducing our power to detect sex differences over time in the primary outcome. Since Exercise-AF recruitment is ongoing, we expect at least an additional 5 participants by the time of publication. It should be noted that 4 females and 10 males enrolled in the Exercise-AF trial were not included in Study 3 as they were randomized to the control group. The unequal ratio for the sample size calculation was chosen considering the: (i) greater risk for AF in males;[120,121] (ii) lower recruitment rate of females in previous clinical trials;[46] and, (iii) student's timeline. This approach has been previously used, yet limitations (e.g., increase in overall sample size, induce bias)[122] suggest it may not be the strongest methodology to conduct sex-based analyses.[51] Finally, our single-centre data has limited generalizability. To establish clear conclusions in sex-specific responses to chronic exercise training in patients with AF, we suggest the pooling of sex-specific data in meta-analyses, and the design of multi-centre, culturally appropriate trials. The latter may mitigate struggles with females' recruitment, achieve equal representation and facilitate the conduction of sex-based analyses.[49,123]

5.7. Conclusion

Contrary to our hypothesis, improvements in $\dot{V}O_{2peak}$ and several physical and mental health outcomes following 12 weeks of exercise training did not differ by sex. Consistent with the literature, females had a lower $\dot{V}O_{2peak}$ (in mL O_2/kg/min) and reported worse AF-specific QoL than males. The sex differences in changes in light physical activity over time deserve further examination. Both females and males with AF and several CVD risk factors were able to engage in 12 weeks of supervised exercise training, as shown by a high adherence and compliance with the exercise prescription.

5.8. References

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5.9. Supplemental material

Appendix 5.1. Consolidated Standards of Reporting Trials (CONSORT): Checklist of items that should be included in reports of randomized controlled trials

Section	Item N.	Description of the Reporting Item
Title and Abstract		
Title	#1a	Identification as a randomized trial in the title.
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions
Introduction		
Background and objectives	#2a	Scientific background and explanation of rationale
Background and objectives	#2b	Specific objectives or hypothesis
Methods		
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	#4a	Eligibility criteria for participants
Participants	#4b	Settings and locations where the data were collected
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	#7a	How sample size was determined.
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines

Randomization – Sequence generation	#8a	Method used to generate the random allocation sequence.
Randomization – Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)
Randomization – Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Randomization – Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.
Blinding	#11b	If relevant, description of the similarity of interventions
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason
Recruitment	#14a	Dates defining the periods of recruitment and follow-up
Recruitment	#14b	Why the trial ended or was stopped
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)
Discussion		
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Registration	#23	Registration number and name of trial registry
Other information		
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Registration	#23	Registration number and name of trial registry
Protocol	#24	Where the full trial protocol can be accessed, if available
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders

Appendix 5.2. Summary of exercise prescription and collection of exercise variables for the Opportunity and Exercise AF trials

Exercise paradigm	**Moderate-intensity continuous training**		**High-intensity interval training**
Research study	OPPORTUNITY trial	Exercise-AF trial	OPPORTUNITY and Exercise-AF
Warm-up	15 min 6-11 RPE	10 min 50% PPO	2 min 50% PPO
Conditioning session	15 to 30 min 67-85% HR_{peak} or 12-16 RPE	40 min 60% PPO	20 min, 2x 8-min blocks: 30s 80-100% PPO + 30s 25% PPO 4 min active recovery b/n blocks
Cool-down	15 min <12 RPE	10 min 25% PPO	1 min 25% PPO
Total duration	60 min	60 min	23 min
Variables collected			
Research study	OPPORTUNITY trial*	Exercise-AF trial*	OPPORTUNITY and Exercise-AF*
Pre-exercise	Resting HR and RPE before the session	Resting HR, BP and RPE before the session	Resting HR, BP and RPE before the session
During exercise	HR and RPE towards the end of the conditioning session	HR, RPE and workload every 5 minutes during the conditioning session	HR and workload every 30 seconds during the conditioning session RPE mid-way and following the last HIIT bout
Post-exercise	-	Resting HR, BP and RPE 5 minutes after the session	Resting HR, BP and RPE 5 minutes after the session

BP: Blood pressure; HR: Heart rate; PPO: Peak power output; RPE: Ratings of perceived exertion (6-20 Borg scale). *Data from different exercise trials was analyzed together.

Appendix 5.3. Sample size calculations to test whether females would experience smaller $\dot{V}O_{2peak}$ improvements over time than males with persistent and permanent atrial fibrillation following 12 weeks of exercise training

Tests for Two Groups of Pre-Post Scores

Numeric Results for Comparing Mean Change in a Repeated Measures Design

Null Hypothesis: $\delta = 0$. Alternative Hypothesis: $\delta \neq 0$
Results assuming a t-test.

Target Power	Actual Power	N1	N2	N	Target R	Actual R	δ	σ(T1)	σ(T2)	ρ	σ(Diff)	Alpha
0.80	0.80834	**36**	**72**	**108**	2.00	2.00	1.8	3.0	3.0	0.500	3.000	0.050

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**N1**	**N2**	**N**	**N1'**	**N2'**	**N'**	**D1**	**D2**	**D**
20%	36	72	108	**45**	**90**	**135**	9	18	27

Appendix 5.4. Baseline and follow-up data of continuous outcomes in patients with persistent and permanent atrial fibrillation

Variables	Females		Males		Time effect	Sex effect	Time* Sex
	Baseline	Follow-up	Baseline	Follow-Up			
Peak aerobic power							
$\dot{V}O_2$peak (mL O_2/kg/min)	14.3 (13.3 to 15.1) (n=34)	16.9 (12.2 to 21.5) (n=12)	19.0 (17.5 to 20.8) (n=75)	21.1 (17.2 to 24.0) (n=31)	**0.011**	**<0.001**	0.707
$\dot{V}O_2$peak (mL O_2/kg of FFM/min)	23.9 (21.2 to 26.4) (n=30)	30.2 (24.2 to 31.6) (n=10)	26.6 (25.0 to 28.8) (n=71)	29.3 (25.2 to 35.3) (n=26)	**0.010**	0.103	0.696
$\dot{V}O_2$peak (L O_2/min)	1.1 (1.0 to 1.3) (n=34)	1.4 (1.1 to 1.8) (n=12)	1.8 (1.7 to 2.0) (n=75)	2.0 (1.7 to 2.2) (n=31)	**0.010**	**<0.001**	0.590
Peak power output (Watts)	110 (100 to 120) (n=34)	140 (120 to 160) (n=17)	148 (140 to 160) (n=76)	180 (160 to 200) (n=33)	**<0.001**	**<0.001**	0.909
AF-specific quality of life (AFSS), points	n=34	n=30	n=75	n=62			
Global well-being (1-10)	8 (7 to 8)	8 (8 to 9)	8 (7 to 8)	8 (8 to 8)	**0.006**	0.669	0.452
Frequency of AF (1-10)	1 (1 to 2)	1 (1 to 2.5)	1 (1 to 1)	1 (1 to 1)	0.672	**0.002**	0.768
Duration of AF (1-10)	1 (1 to 2)	1 (1 to 5)	1 (1 to 1)	1 (1 to 1)	0.196	**0.005**	0.224
Severity of AF (1-10)	4 (2.5 to 5.5)	4.5 (2 to 5.5)	3.5 (2 to 4.5)	2 (1.5 to 3)	0.089	**0.041**	0.084
Visits to the emergency department	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.429	0.405	0.522
Hospitalizations	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.239	0.692	0.576
Specialist visits	1.5 (1 to 2)	1 (0 to 1)	1 (1 to 1)	1 (0 to 1)	0.103	0.506	0.770
Total burden (0-30)	21.5 (20 to 24.5)	21 (14.5 to 25)	22 (21 to 23.25)	21 (21 to 21.5)	**0.004**	0.154	0.413
Symptom score (0-35)	8 (6 to 11.5)	8 (4 to 10)	7 (5.5 to 8.5)	6 (5 to 7)	**0.002**	0.144	0.271
General quality of life (SF-36), points	n=34	n=30	n=75	n=63			
Physical functioning	45.8 (39.3 to 48.0)	48.0 (41.5 to 50.2)	45.8 (42.6 to 48.0)	48.0 (45.8 to 52.4)	**0.007**	0.553	0.294
Role limitations - physical	40.8 (33.4 to 48.2)	44.5 (33.4 to 55.6)	48.2 (40.8 to 51.9)	48.2 (40.8 to 55.6)	0.229	0.670	0.619
Bodily pain	34.9 (33.7 to 39.6)	35.2 (34.9 to 35.4)	35.4 (34.9 to 40.0)	34.9 (34.9 to 35.4)	0.335	0.462	0.459
General health	48.2 (43.9 to 52.4)	48.7 (42.5 to 51.1)	42.5 (40.0 to 47.4)	47.4 (42.5 to 49.9)	0.273	0.108	0.333
Vitality	45.9 (44.7 to 51.9)	48.3 (44.7 to 51.9)	47.1 (44.7 to 49.5)	47.1 (44.7 to 51.9)	0.215	0.671	0.086
Social functioning	51.7 (46.2 to 57.3)	57.3 (51.7 to 57.3)	54.5 (51.7 to 57.3)	51.7 (51.7 to 57.3)	0.066	0.927	0.278
Role limitations - emotional	55.7 (55.7 to 55.7)	55.7 (55.7 to 55.7)	55.7 (55.7 to 55.7)	55.7 (55.7 to 55.7)	0.152	0.588	0.855
Mental health	55.1 (46.2 to 56.2)	55.1 (48.4 to 57.3)	52.9 (50.6 to 55.1)	55.1 (52.9 to 57.3)	0.221	0.629	0.570
Physical component summary	39.9 (36.0 to 43.4)	41.9 (37.3 to 45.1)	38.9 (38.1 to 42.1)	42.5 (41.6 to 43.7)	0.280	0.874	0.678
Mental component summary	57.0 (52.0 to 59.4)	55.2 (53.3 to 58.3)	58.8 (51.7 to 60.1)	56.3 (53.8 to 58.8)	0.150	0.876	0.588

Functional capacity	n=33	n=29	n=70	n=59			
6-minute walk test distance (m)	506 (464 to 552)	516 (484 to 566)	534 (500 to 569)	571 (530 to 583)	**0.001**	0.159	0.466
Hemodynamic and anthropometric data	n=34	n=30	n=77	n=64			
Resting heart rate (bpm)	77 (73 to 84)	74 (71 to 81)	69 (66 to 73)	67 (62 to 70)	**0.025**	**0.001**	0.524
Resting systolic BP (mmHg)	120 (117 to 128)	121 (114 to 131)	126 (122 to 129)	124 (119 to 130)	0.666	0.535	0.844
Resting diastolic BP (mmHg)	79 (73 to 81)	79 (76 to 82)	77 (72 to 80)	79 (75 to 81)	0.280	0.665	0.496
Body mass (kg)	76.3 (72.3 to 84.0)	75.2 (67.9 to 84.6)	94.3 (90.5 to 96.8)	94.4 (88.5 to 97.7)	0.081	**<0.001**	0.772
Body mass index (kg/m^2)	28.7 (25.8 to 32.5)	27.4 (24.5 to 32.5)	30.3 (28.3 to 30.8)	29.9 (28.1 to 30.9)	0.067	0.741	0.673
Waist circumference (cm)	91.6 (83.1 to 100.0)	88.0 (80.1 to 97.0)	107.0 (104.0 to 109.5)	105.5 (101.8 to 109.2)	**0.037**	**<0.001**	0.398
Body fat (%)	38.3 (33.3 to 39.1)	37.6 (30.4 to 40.9)	27.8 (25.7 to 29.4)	27.6 (26.0 to 30.4)	0.126	**<0.001**	0.209
Fat mass (kg)	29.2 (25.1 to 32.72)	26.7 (20.2 to 33.8)	25.9 (22.7 to 28.0)	27.3 (22.5 to 28.9)	0.269	0.360	0.540
Fat-free mass (%)	61.7 (60.9 to 66.7)	62.4 (59.1 to 69.4)	72.2 (70.6 to 74.3)	72.4 (69.6 to 73.9)	0.722	**<0.001**	0.908
Fat-free mass (kg)	45.5 (43.2 to 49.0)	44.8 (42.5 to 50.1)	67.4 (64.5 to 69.6)	66.0 (64.0 to 69.4)	0.126	**<0.001**	0.209
Anxiety and depression	n=20	n=23	n=38	n=44			
Anxiety (points)	5 (4 to 6)	4 (3 to 5)	4 (3 to 5)	4 (3 to 6)	**0.018**	0.425	0.734
Depression (points)	2 (1 to 5)	1 (1 to 2.5)	4 (2 to 6)	2.5 (2 to 4)	**<0.001**	0.372	0.808
Device-measured physical activity	n=33	n=29	n=69	n=60			
Light physical activity (min/week)	2,192 (1,907 to 2,664)	2,137 (1,772 to 2,275)	1,793 (1,686 to 2,032)	1,989 (1,818 to 2,132)	0.659	**0.016**	**0.034**
Moderate physical activity (min/week)	104 (58 to 164)	154 (72 to 190)	105 (90 to 151)	136 (116 to 180)	0.329	0.605	0.621
Vigorous physical activity (min/week)	0 (0 to 0.6)	0 (0 to 0)	0 (0 to 0)	0 (0 to 1.2)	0.531	0.948	0.760
Moderate- to vigorous-physical activity (min/week)	112 (58 to 152)	154 (72 to 195)	105 (91 to 152)	137 (119 to 184)	0.364	0.625	0.635
Step counts per week	24,991 (21,181 to 32,652)	31,228 (26,585 to 40,591)	28,503 (24,575 to 30,305)	31,954 (27,211 to 36,211)	0.055	0.816	0.784

Data presented as median (95% confidence interval). P<0.05 denotes significance. AF: Atrial fibrillation; BMI: Body mass index; BP: Blood pressure; FFM: Fat-free mass; MVPA: Moderate- to vigorous-intensity physical activity; $\dot{V}O_{2peak}$: Peak aerobic power.

CHAPTER 6 - Sex differences in the change in peak aerobic power and additional physical and mental health outcomes following exercise training in adults with atrial fibrillation: a systematic review and meta-analysis

PREAMBLE TO STUDY 4

This final article pools available evidence of exercise trials in patients with atrial fibrillation using a sex-specific lens to provide a comprehensive examination of potential sex differences in improvements in physical and mental health outcomes following exercise training. Since 2013, more than ten systematic reviews and meta-analyses in the atrial fibrillation literature have evaluated the health benefits of chronic exercise training to manage patients with cardiovascular disease risk factors (e.g., $\dot{V}O_{2peak}$, body mass) and improve quality of life, yet none have compared the results by sex.

6.1. Abstract

Background: Patients with atrial fibrillation (AF) present with poor peak aerobic power ($\dot{V}O_{2peak}$), quality of life (QoL) and physical and mental health. Improving $\dot{V}O_{2peak}$ through exercise training (ET) is important for patients with AF, as it is associated with lower mortality rates. In patients with cardiovascular disease, smaller $\dot{V}O_{2peak}$ improvements have been reported in females than males following ET. This sex-response difference has not been examined in patients with AF. **Aims:** To compare changes in $\dot{V}O_{2peak}$ following ET between females (F) and males (M) with AF. Secondary aims compared changes in patient AF symptoms, QoL and additional physical and mental health outcomes. **Methods:** Five bibliographic databases were searched to identify prospective studies implementing ET (≥4 weeks) in adults with AF, and that reported a baseline and follow-up measure of ≥1 primary or secondary outcome. The mean difference (MD) in the change following ET was compared between sexes using random-effects meta-analyses. **Results:** Our search identified 9,398 studies. Sex-specific data were obtained from 18 of 60 eligible studies, with 868 participants enrolled in an exercise training program (29% F, F: 69±7, M: 66±8 years old). ET was 6 weeks to 1 year in duration, and mostly combined aerobic and resistance training of moderate to vigorous intensity, 2 to 6 days/week. $\dot{V}O_{2peak}$ changes did not differ between sexes (MD=+0.22, 95% CI -1.13 to +1.57 mL O_2/kg/min, p=0.75; I^2 27%). AF severity (MD=+1.00, 95% CI +0.13 to +1.87 points; I^2 0%), general health perceptions (MD=-3.71, 95% CI -6.88 to -0.55 points; I^2 22%) and systolic blood pressure (MD=+3.11, 95% CI +0.14 to +6.09 mmHg; I^2 42%) improved less in females. **Conclusions:** We addressed the lack of sex-based analyses in previous ET studies in patients with AF. Changes in $\dot{V}O_{2peak}$ did not differ between sexes. Smaller improvements were observed in AF severity, general health and blood pressure in females with AF. Females are underrepresented in ET trials (<30%) when compared to the disease sex distribution globally (F: 47%).

6.2. Introduction

Atrial Fibrillation (AF) is characterized by an irregular cardiac rhythm and rapid heart rate (HR). More than 37 million adults have AF globally,[1,2] and a 60% increase in AF prevalence is expected by 2050.[2] AF is typically a progressive disorder (i.e., paroxysmal to persistent, to long-standing persistent and finally permanent) partly due to the presence of modifiable cardiovascular disease (CVD) risk factors (e.g., hypertension, obesity).[3,4] Patients with AF have a 1.6 to 5.0 mL O_2/kg/min lower peak aerobic power ($\dot{V}O_{2peak}$) than other CVD populations, including ischemic heart disease, valvular disease and heart failure.[5–7] In turn, this may be why they are bothered by a low exercise tolerance.[8] Exercise training may increase their $\dot{V}O_{2peak}$, and this could have clinical implications: improving $\dot{V}O_{2peak}$ with exercise-based cardiovascular rehabilitation (CR) has been associated with a lower risk for AF recurrence (a 1 metabolic equivalent [MET; i.e., 3.5 mL O_2/kg/min] increase in $\dot{V}O_{2peak}$ has been shown to reduce AF recurrence by 9%),[9] and a 12 to 17% lower risk for CVD hospitalization, all-cause mortality and morbidity.[10,11] A meta-analysis in patients with AF revealed increases in $\dot{V}O_{2peak}$ (n=3 studies, mean difference [MD+1.6 mL O_2/kg/min, 95% confidence interval [CI] 0.1 to 3.1, p=0.04, I^2 82%), general quality of life (QoL) (n=3 studies, SF-36 mental component summary [MCS]: MD=+4.0, 95% CI +0.3 to +7.7, p=0.04, I^2 62%, physical component summary [PCS]: MD=+1.8, 95% CI +0.1 to +3.6, p=0.04, I^2=26 %) and functional capacity as measured by the 6-minute walk test [6MWT] (n=3 studies, MD=+46.9 m, 95% CI 26.4 to 67.4, p<0.001, I^2 66%) following various exercise programs when compared to control (i.e., non-exercise usual care).[12] However, such increases did not reach clinical significance.

Sex differences in the AF patient presentation, treatment and outcomes should be considered in the design, analysis and reporting of research trials.[13,14] Females with AF have a substantially lower $\dot{V}O_{2peak}$ than males.[15] Females' lower $\dot{V}O_{2peak}$ and physical activity

levels[16] may partly explain their reporting of more frequent and severe AF symptoms (e.g., dyspnea, fatigue, palpitations, dizziness, anxiety),[17–19] poorer QoL[20,21] and greater risk of mortality when compared to males.[2] Improving $\dot{V}O_{2peak}$ through exercise training represents an important fitness target for patients with AF, which may particularly benefit females. For instance, results from the CopenHeartRFA trial suggest that CR may narrow pre-existing differences in AF-specific QoL between sexes.[15] Yet, emerging research in healthy and CVD populations indicates that females may experience smaller gains in $\dot{V}O_{2peak}$ than males following the same aerobic exercise programs between 7 to 52 weeks in duration (e.g., MD=1.95 mL O_2/kg/min smaller increase in females; e.g., F: 13% vs. M: 17% improvement, $p<0.001$).[22–26] None of the systematic reviews to date in patients with AF have examined sex differences in the chronic (≥4 weeks) responses to exercise training.[14]

There are sex differences in additional modifiable CVD risk factors in patients with AF. The prevalence of hypertension,[19,20,27] obesity[16] and depression[16] is often higher in females than males with AF. Females also experience faster HRs during AF,[28] which may accelerate the electrical and structural remodeling in the atria.[29] Such risk factors contribute to AF pathogenesis and AF progression,[29] but growing evidence supports the benefits of exercise training in improving physical and mental health and managing these patient CVD risk factors.[30,31] In patients with AF, whilst exercise alone may not improve resting blood pressure,[6,32–35] it has been shown to reduce resting HR,[6,33,36–38] body mass,[37] fat mass,[5,33] and anxiety and depressive symptoms.[32,39] Few AF studies have examined changes in physical activity levels with exercise training.[35,37,40,41] Improvements in moderate- to vigorous-intensity physical activity (MVPA) levels following 12 weeks of high-intensity interval training (HIIT) and moderate- to vigorous-intensity continuous training (MICT) have been reported.[37,41] Although some exercise studies did not find significant improvements in MVPA.[35,40] Less is known regarding sex differences in the changes in these outcomes with

exercise training.[15] In patients with CVD, findings have been inconsistent.[24–26,42,43] Our meta-analysis in patients with coronary artery disease revealed smaller reductions in body mass index (BMI) in females than males following HIIT.[43] Notably, there was an eightfold lower number of females (F: 103, M: 836).[43]

The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS/CHRS) comprehensive guidelines for the management of patients with AF were the first to incorporate specific exercise targets for this population.[4] Many research gaps remain regarding potential sex differences in the chronic response to exercise training in the AF population.[14] To address the scarce sex segregation of previous evidence from exercise trials in patients with AF,[13] the Sex and Gender Equity in Research (SAGER) guidelines suggest pooling sex-specific data of studies for performing meta-analyses.[44,45]

6.3. Objectives and hypotheses

The primary purpose of this systematic review and meta-analysis was to compare changes in $\dot{V}O_{2peak}$ following exercise training between females and males with AF. We hypothesized that females with AF would experience smaller improvements in $\dot{V}O_{2peak}$ than males. The secondary aim was to compare changes in AF symptoms, AF-specific and general patient QoL, and additional physical and mental health outcomes (i.e., functional capacity, resting HR and blood pressure, BMI, body composition, anxiety and depressive symptoms, physical activity levels) between sexes following exercise training.

6.4. Methods

Study design and registration

This systematic review adhered to the reporting guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses statement[46] (PRISMA, see Appendix 6.1.) and the SAGER guidelines.[45] The review methodology was registered in the international prospective register of systematic reviews (PROSPERO) in February 2022 (# CRD42022302310).[47]

Study eligibility criteria

Study designs

Prospective experimental designs (randomized controlled trials [RCTs], quasi-experimental, pre-post, and case-control studies) were eligible.

Population

Studies were included if the sample comprised of adults (≥18 years old) with an AF diagnosis, and where data from adults with AF could be extracted (i.e., ≥10% of the sample had AF).

Interventions

Studies had to implement exercise training for at least 4 weeks.[48] Exercise was defined as a structured, planned and repetitive subset of physical activity with the aim to maintain or improve physical fitness and health.[49] Multi-component interventions (e.g., combination of nutrition, stress management, strict medication control) were eligible as long as they included exercise training. There were no restrictions on the intensity or type of exercise training (e.g., aerobic training, circuit training, body weight or machine-based resistance training, isometric exercises, Yoga, dancing), mode of delivery (e.g., in person, virtual, hybrid) or setting of the intervention (e.g., home-based, in hospital, in the community, individual or as a group).

Outcomes

Eligible studies had to report a baseline and follow-up measure for at least one primary or secondary outcome. The primary outcome was peak aerobic power, defined as the highest

value of oxygen consumption ($\dot{V}O_{2peak}$) attained during an exercise test designed to bring the participant to volitional fatigue,[50] or estimated from a submaximal exercise test.[51] Directly measured or estimated (in mL O_2/kg/min or METs) $\dot{V}O_{2peak}$ was, therefore, considered for inclusion. Secondary outcomes included patient-reported outcomes and objective measures: self-reported AF symptom frequency and/or severity, self-reported AF-specific and general QoL, functional capacity, resting HR and blood pressure, BMI, body composition, self-reported anxiety and depression, and physical activity levels (self-reported or device-measured). Additional outcomes of interest included: adherence (i.e., number of sessions attended by participants), dropout rates and adverse events during the study period.

Publication status and language

Published peer-reviewed journal articles, non-peer reviewed grey literature including published theses and dissertations, conference abstracts, presentations, and proceedings were included. Unpublished data were also included. No language restrictions were imposed on the search, but only papers written in English, French, Japanese, Portuguese, or Spanish were included – as per authors' language expertise.

Search strategy

A comprehensive search strategy from an existing systematic review was re-used to identify relevant studies.[52] This search was previously designed and translated according to the indexing systems of several databases in collaboration with a medical research librarian (NL). The search was previously peer reviewed by a second research librarian. Medical subject headings (MeSH) and keywords related to "atrial fibrillation", "exercise training" and "cardiac rehabilitation" were used. A draft of the search strategy used for each database is provided in Appendix 6.2. No date restrictions were imposed. Five electronic bibliographic databases were searched from inception to January 31st, 2022: CINAHL (EBSCOhost); Cochrane Library (Wiley); Embase (OvidSP); MEDLINE (OvidSP); and PycINFO (Ovid).

Registries (i.e., ClinicalTrials.gov and PROSPERO) were searched to identify recently completed trials and systematic reviews. Conference proceedings of the two previous years related to patients with AF and exercise training were searched to identify further studies.

Data management and selection of eligible studies

The results from the search strategy were uploaded into the Covidence Systematic Review Software (Veritas Health Innovation, Australia). Duplicate articles were removed using the "duplicate" function or manually. Two independent reviewers (SVA, IRM) screened the titles and abstracts of all articles against the inclusion criteria. Full texts of each potentially relevant article were uploaded on Covidence and screened by two independent reviewers (SVA, IRM) to determine eligibility. Disagreements were resolved by discussion with a third reviewer (JLR). The authors were not blinded to the study authors or journal titles.

Data extraction

A data extraction form was created using Microsoft Excel (Microsoft Canada Inc. Mississauga, ON, Canada).[47] Data extracted from each eligible study, when available, included: publication details (authors, country and year of publication), participant characteristics by sex (sample size, sex distribution, AF type, mean age, sociodemographic and gender-related variables [e.g., ethnicity, marital status, education, employment, income], prescribed medications, medical conditions and procedures), study design, characteristics of the assessment of $\dot{V}O_{2peak}$ (test protocol, modality, method of measurement), details of exercise interventions (frequency, intensity, time, type, [FITT], volume and progression), participant adherence with the exercise intervention (number of sessions attended), number of adverse events during the study period, dropouts, and description of the control group, if any. In addition, the means and standard deviations (SD) of primary and secondary outcomes measured at baseline and following the exercise intervention were extracted by a reviewer and verified by a second reviewer (SVA, JW, TT). Study authors were contacted to resolve

any uncertainties and for missing information. If studies included both sexes but failed to report outcomes by sex, the corresponding authors were contacted by SVA to obtain sex-specific data. The approach to contact authors involved up to three emails.[53] Receptive authors were provided the data extraction form and received up to three follow-up emails as reminders, after which they were considered unwilling or unable to share their data. Authors of studies which reported on collecting a measure of interest but did not report the outcome on the manuscript were contacted to provide their unpublished data using the same approach.

Methodological quality and risk of bias within studies

The TESTEX scale was used to examine the quality and risk of bias of each study separately by two reviewers (SVA and IRM) not blinded to the authors or journals. Any disagreements were resolved by consensus and/or discussion with a third reviewer (JLR). The TESTEX scale uses 12 criteria (some of which can score more than one point) for a maximum score of 15 points, five points pertain to *study quality*: (1) eligibility criteria specified, (2) randomization specified, (3) allocation concealment, (4) groups similar at baseline, and (5) blinding of assessor for the primary outcome; and 10 points pertain to *study reporting*: (1) outcome measures assessed in 85% of patients (up to 3 points possible), (2) intention-to-treat analysis, (3) between-group statistical comparisons reported, (4) point measures and measures of variability for all reported outcome measures (up to 2 points possible), (5) activity monitoring in control groups, (6) relative exercise intensity remained constant and (7) exercise volume and energy expenditure. A score <10 was considered low quality.[12] The TESTEX has shown good reliability to assess the quality and reporting of exercise training trials.[54] The inter-observer reliability, assessed as the level of agreement between observers with the Cohen Kappa statistic, ranged between 0.44 - moderate and 1.00 - almost perfect in all criteria, without significant differences between observers.[54]

Assessment of overall quality of the evidence

The quality of the evidence for the included studies was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[55] approach by one reviewer (SVA) and verified by a second reviewer (IRM). GRADE classifies the evidence as high, moderate, low or very low depending on: (1) risk of bias within individual studies; (2) inconsistency of results between studies; (3) indirectness of evidence; (4) imprecision; and, (5) publication bias. RCT evidence represents the highest quality rating. The scores for downgrading the quality of the evidence were rated as 0 points (not serious), -0.5 points (not serious, borderline), or - 1 point (serious). Points were combined across domains to yield a total score. If the final scoring resulted in a half-point, the quality was downgraded.

Quantitative data synthesis and planned analyses

Measures of treatment effect

Meta-analyses were performed using the Comprehensive Meta-Analysis Software (Biostat Inc. Version 4, US). Baseline and follow-up values of continuous outcomes were entered in the software by sex. Pooled estimates of the effect of exercise training on $\dot{V}O_{2peak}$ for females when compared to males (i.e., the MD of the $\dot{V}O_{2peak}$ change in females vs. males following exercise training) were obtained using a random-effects model, since effect sizes were not expected to be identical across all studies.[56] The same approach was used for the secondary outcomes. Where possible, pooled estimates were also calculated in each sex separately for the changes in $\dot{V}O_{2peak}$ and secondary outcomes following exercise training when compared to a non-exercise control group. A quantitative synthesis of the measures of effect and 95% CI are presented in the form of forest plots. For outcomes where a quantitative synthesis was not appropriate, a narrative synthesis was presented following the Synthesis Without Meta-analysis guidelines.[57] Categorical data are presented descriptively.

Pre-specified additional analyses

When sufficient data were available, several sub-analyses were performed to identify whether participant or intervention characteristics may have influenced the effects of exercise training in females compared to males. We planned to create sub-groups considering differences in: (i) participant characteristics (e.g., age, AF type, co-morbidities); (ii) exercise program characteristics (FITT principles); (iii) method of $\dot{V}O_{2peak}$ measurement (estimated vs. measured); (iv) method of exercise prescription (e.g., HR or ratings of perceived exertion [RPE] ranges); and, (v) adherence with the program.

Assessment of heterogeneity and publication bias

The degree of inconsistency across studies was quantified using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 values of <30%, 30-60% and >60% were classified as low, moderate and high heterogeneity, respectively.[58] Funnel plots were visually inspected to assess the effect of publication bias on our systematic review. Publication bias was absent if plots resembled a symmetrical inverted funnel, or present if they were skewed with an asymmetrical shape. Further, an Egger's test $p<0.10$ indicated the presence of a significant publication bias.[59]

6.5. Results

Our search identified 9,398 records (see Figure 6.1.). Of these, 843 were retrieved through CINAHL, 570 through Cochrane, 5,924 through Wiley EMBASE, 1,954 through MEDLINE, 103 through PsycINFO, and four through Dissertations and Theses. Of these records, 2,482 duplicates were removed and the titles and abstracts of 6,916 studies were screened. Of the 115 full texts screened, a total of 60 studies were considered eligible (see Figure 6.1. for exclusions). Sex-specific data were obtained from 18 of the 60 eligible studies: one article reported outcomes segregated by sex,[15] two studies included only males[60,61] and 15 authors made their raw data available by sex.[32,35,37,39,41,62–72] Upon contacting authors to obtain the

sex-specific data, 20 did not respond to the email or their contact information was incorrect and could not be found, nine authors were unable to locate or access their data, seven were interested in sharing the data but did not eventually provide, three investigators cited ethics-related restrictions for data sharing, and three were unable to provide data for other reasons (see Figure 6.1.).

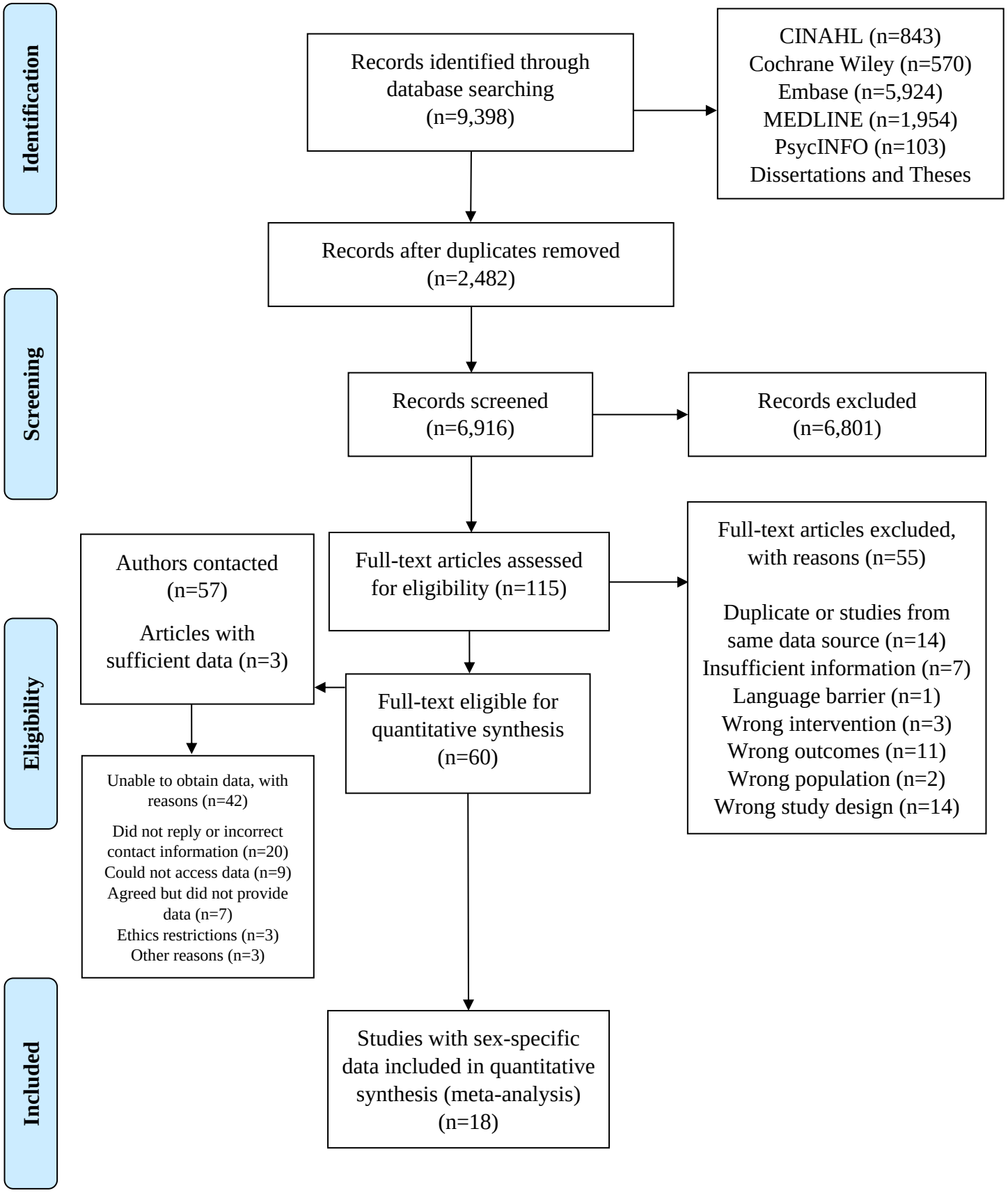


Figure 6.1. PRISMA flow diagram. PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Trial characteristics

A total of 18 studies published between 2016 and 2022 were included (see Table 6.1.). Most (n=16) studies were RCTs, of which 13 were single-centre[15,37,39,41,60–62,64,65,68,69,72,73] and three were multi-centre.[35,67,70] Two studies used a pre-post design.[32,63] The majority (n=13) of trials compared exercise training with non-exercise usual care,[15,37,39,60–64,67–70,73] four studies compared different exercise training programs (e.g., HIIT vs. MICT),[35,41,65,72] and two studies had only one exercise group without a comparison.[32,63] Studies were conducted in Brazil (n=1), Canada (n=2), China (n=1), Denmark (n=2), Japan (n=2), Netherlands (n=1), Norway (n=1), Poland (n=1), Portugal (n=1), Russia (n=1), Sweden (n=1) and the United Kingdom (n=4). The data of two published abstracts without accompanying full texts were included.[61,63] All included manuscripts and abstracts were published in English.

The duration of the exercise programs ranged from 6 weeks to 1 year, with most protocols including 20- to 65-minutes of aerobic and resistance training sessions of moderate to vigorous intensity, 2 to 6 days per week (see Table 6.1.). Half of the studies focused primarily on exercise training,[35,37,41,60,61,63,66,69] while the remaining combined exercise with additional treatments such as education[15,32,39,64,65,72] and nutrition sessions.[64] Most studies had a frequency of exercise sessions of 2 to 3 days per week. Many interventions were 12 weeks in duration and performed on a cycle ergometer or treadmill. Seven studies implemented exercise training in the form of walking.[35,37,61,62,64,67,68] The intensity of five,[62,65,70,72,73] four[15,35,41,64] and six[35,37,39,41,60,69] exercise interventions fell within the moderate, moderate- to vigorous-and vigorous range, respectively. Supervised, outpatient exercise training was frequently implemented, yet seven studies combined in-hospital supervised sessions with home-based unsupervised exercise,[15,35,37,62,64,65,72] and two studies were home-based.[67,68] Continuous aerobic exercise was most frequently prescribed, and seven studies mentioned some use of interval training in the description of their intervention.[35,37,39,41,64,69,73] Of these,

HIIT was implemented by four studies,[35,37,41,69] and one trial prescribed moderate- to vigorous-interval training.[64] Seven studies combined several methods to prescribe exercise intensity (i.e., HR, RPE, peak power output [PPO], anaerobic threshold),[15,37,39,41,63,72,73] two used RPE,[35,60] one used the Talk Test[70] and three based their exercise prescription on HR ranges.[64,65,69] Several studies incorporated alternative strategies to enhance adherence to exercise training such as the use of mobile apps,[65] regular phone calls[72] and contact with a nurse during the study period.[15,67,68,70]

Table 6.1. Trial characteristics of the studies included in the systematic review.

Study details	Target population	Exercise intervention: (F)requency, (I)ntensity, (T)ime, (T)ype, (P)rogression and (S)etting	Prescription method	Control group	Relevant outcomes and $\dot{V}O_{2peak}$ measurement method
Alves *et al.*, 2022, Brazil Single-centre RCT ClinicalTrials # NCT03550872	Permanent AF with HFrEF	**CR:** **F:** 3 d/week **I:** Vigorous **T:** 60 min/session, 12 weeks **T:** Combined continuous aerobic training on a cycle ergometer (40 min) with resistance training targeting major muscle groups (10 min) **P:** W adjusted to maintain the RPE within range throughout program **S:** In-hospital (supervised)	RPE (Borg Scale): 14-16 points	**Control:** Usual care	$\dot{V}O_{2peak}$ (mL/kg/min): CPET on a cycle ergometer with direct breath-by-breath analysis **QoL:** HF-specific QoL (MLHFQ) **Physical:** Resting systolic, diastolic BP, HR, BMI **Measurement timepoints:** Baseline and 3-month follow-up
Bittman *et al.*, 2022, Canada Single-centre RCT ClinicalTrials # NCT03724383	Non-permanent AF with BMI ≥27 kg/m^2 or a high-risk waist circumference	**CR:** Phase I (6 months): Months 1-4: Nutrition: 14 dietician-led nutrition sessions in the community Exercise: **F:** 3 to 5 d/week **I:** Moderate-to-vigorous **T:** 20 to 40 min/session, target 200 min/week **S:** Home-based (unsupervised) Months 5-6: **F:** 2 d/week **I:** Low-to-vigorous **T:** 60 min/session **T:** Combined 20-min interval training and 10-min resistance training of low intensity + education **S:** In-hospital (supervised) Phase II (6 months): home-based maintenance exercise; ≥30 min, 5 d/week. Optional walking group	HR: Work: 5x2 min at 65-85% HR_{peak} Recovery: 5x2 min at 60-65% HR_{peak}	**Control:** Both groups received a Fitbit, guideline-based AF care (including information regarding safe exercises for AF at home) and information on food and PA Guidelines	**Estimated $\dot{V}O_{2peak}$** (METs): symptom-limited exercise stress test on a treadmill without ergospirometry **QoL:** AF-specific (AFSS) and General (SF-36) **Physical:** Resting systolic and diastolic BP, BMI, body fat **Mental:** Anxiety (GAD-7) and Depression (PHQ-8) **Measurement timepoints:** Baseline, 6 and 12-month follow-up

Borland *et al.*, 2020, Sweden Multi-centre RCT ClinicalTrials # NCT02493387	Permanent AF	**<u>CR (INT1):</u>** **F:** 4 d/week **I:** Moderate-to-vigorous **T:** 60 min/session, 12 weeks **T:** Combined HIIT on a cycle ergometer, circuit training and machine-based resistance training **S:** 2 d/week in-hospital (supervised), 2 d/week home-based (unsupervised) **<u>PA prescription (INT2):</u>** **F:** 4 d/week **I:** Moderate-to-vigorous **T:** 40-min/session, 12 weeks **T:** walking (recorded on a diary) **S:** Unsupervised	RPE (Borg Scale): **INT1:** Work: 4x2 min at 13-17 points Recovery: 4x2 min at 13 points **INT2:** 13-15 points	-	**QoL:** General QoL (SF-36) **Physical:** Resting systolic and diastolic BP, HR, BMI **PA levels:** Self-reported (IPAQ) and device-measured (triaxial accelerometer) **Adherence:** % exercise sessions attended **Measurement timepoints:** Baseline and 3-month follow-up
Cai *et al.*, 2022, China Single-centre RCT ClinicalTrials # NCT 04414007	Patients who underwent ablation for AF	**<u>Telerehabilitation (INT1)</u>:** **Conventional CR:** **I:** Moderate **T:** 65 min/session, target ≥150 min/week, 12 weeks **T:** Combined aerobic and resistance training + <u>education</u> **S:** In-hospital (supervised) + home-based **+ Telemedicine:** Individualized prescription of aerobic + resistance + flexibility + balance, videos, ECG monitor and staff communication with mobile apps (Shukang™ and Binglijia™) **<u>Conventional CR (INT2)</u>:** **I:** Moderate **T:** 65 min/session, target ≥150 min/week, 12 weeks **T:** Combined aerobic and resistance training + <u>education</u> **S:** In-hospital (supervised)	HR: $(HR_{peak} - HR_{rest}) \times (40\text{-}60)\% + HR_{rest}$	-	$\dot{V}O_{2peak}$ (mL/kg/min): CPET with direct breath-by-breath analysis **QoL:** General QoL (SF-36) **Physical:** Resting systolic and diastolic BP, HR, BMI, functional capacity (6MWT) **PA levels:** Self-reported (IPAQ) **Adherence:** % of the 12 weeks when ≥150 min/week of PA were met **Measurement timepoints:** Baseline and 3-month follow-up

Dabrowski *et al.*, 2018, Poland Single-centre RCT	Patients with permanent AF, HFrEF and CIED	**CR:** **F:** 3 d/week **I:** Moderate **T:** 60 min/session, 6 months **T:** Combined aerobic (interval cycle ergometer 55-64 rpm for 30 min) and resistance (10-12 reps per exercise, 5-10 min) **S:** In-hospital (supervised)	HR and RPE: Aerobic: 40% of Karvonen formula, or 3-4/10 RPE Resistance: ≤ 50% 1 RM, RPE ≤11-12	**Control:** No exercise (NR)	**$\dot{V}O_{2peak}$** (mL/kg/min): CPET with direct breath-by-breath analysis **Mental:** Depression (Beck Depression Inventory) **Measurement timepoints:** Baseline and 6-month follow-up
Dalal *et al.*, 2019, REACH-HF study, UK Multi-centre RCT ISRCTN registration # ISRCTN86234930	AF with HFrEF	**CR:** Home-based program; patients went over the manual for 12 weeks with the assistance of a nurse (a few face-to-face and telephone contacts): 1. Progressive individualized exercise training delivered as a walking program, a chair-based exercise DVD or a combination (target ≥3 d/week, recorded in a diary) 2. Managing stress, breathlessness 3. HF symptom monitoring 4. Taking medications 5. Understanding HF	NR	**Control:** Usual medical care as per HF management guidelines, including specialist HF nurse care (no participation in CR)	**QoL:** HF-specific QoL (MLHFQ) **Physical:** Functional capacity (ISWT) **Mental:** Anxiety and Depression (HADS) **PA levels:** Device-measured (GeneActiv accelerometer) **Adherence:** Attend the first face-to-face contact with the facilitator and at least two facilitator contacts thereafter **Measurement timepoints:** Baseline, 4, 6 and 12-month follow-up
Joensen *et al.*, 2019, Denmark Single-centre RCT ClinicalTrials # N-20120002	Non-permanent AF	**CR:** **F:** 2 d/week **I:** Vigorous **T:** 60 min/session, 12 weeks **T:** Combined aerobic (≥30 min/session) and interval resistance training. Encouraged to do moderate PA ≥30 min/d Education: 1h, 1 d/week for 8 weeks **S:** In-hospital (supervised); group-based (10 patients)	RPE (Borg scale) and $\dot{V}O_{2peak}$: RPE 14-16 and ≥70% $\dot{V}O_{2peak}$	**Control:** Advised to continue their usual lifestyle	**Estimated $\dot{V}O_{2peak}$:** Maximum cycle ergometer test without ergospirometry **QoL:** AF-specific QoL (AFEQT) **Physical:** Resting systolic, diastolic BP, HR **Mental:** Anxiety (GAD-7) and Depression (PHQ-9) **Measurement timepoints:** Baseline, 3, 6 and 12 months
Kato *et al.*, 2019, Japan	Patients with persistent AF who did not develop AF	**CR:** **F:** 3-5 d/week **I:** Moderate **T:** 60 min/session, 6 months	Aerobic: below the anaerobic threshold	**Control:** Advised to continue their usual lifestyle	**$\dot{V}O_{2peak}$** (mL/kg/min): CPET with direct breath-by-breath analysis on a cycle ergometer. Measured in the CR group only.

Single-centre RCT	in the first month after catheter ablation	**T:** Combined aerobic (30 min of cycling or walking) and machine-based resistance training (2-3 sets of 3 upper and 5 lower-extremity exercises) **S:** In-hospital (supervised) 1-2 d/week, home-based (unsupervised) 2-3 d/week	Resistance: 40%-60% 1RM		**Physical:** Functional capacity (6MWT) **Measurement timepoints:** Baseline and 6-month follow-up
Lang *et al.*, 2018, REACH-HFpEF study, UK Single-centre RCT ISRCTN # 78539530	AF and HFpEF	**CR:** Home-based program; patients went over the manual for 12 weeks with the assistance of a nurse (a few face-to-face and telephone contacts): 1. Progressive individualized exercise training delivered as a walking program or a chair-based exercise DVD or a combination (target ≥3 d/week, recorded in a diary) 2. Managing stress, breathlessness 3. HF symptom monitoring 4. Taking medications 5. Understanding HF	NR	**Control:** Usual medical care as per HF management guidelines, including specialist HF nurse care (no participation in CR)	**QoL:** HF-specific QoL (MLHFQ) **Physical:** Functional capacity (ISWT) **Mental:** Anxiety and Depression (HADS) **PA levels:** Device-measured (GeneActiv accelerometer) **Adherence:** Attend the first face-to-face contact with the facilitator and at least two facilitator contacts thereafter) **Measurement timepoints:** Baseline, 4 and 6-month follow-up
Makhinova *et al.*, 2017, Russia Single-centre RCT ClinicalTrials # NCT04511520	Patients with paroxysmal AF who underwent ablation	**CR:** **F:** 2-3 d/week **T:** 6 months **T:** Walking, stretching and breathing exercises **S:** In-hospital (supervised)	NR	**Control:** Usual care	**Estimated $\dot{V}O_{2peak}$** (3.5 ml/kg/min + walking speed during 6MWT x 0.1) **Physical:** Resting systolic and diastolic BP, HR, BMI **Mental:** Anxiety and Depression (HADS) **Measurement timepoints:** Baseline and 6-month follow-up
Malmo *et al.*, 2016, Norway Single-centre RCT ClinicalTrials # NCT01325675	Non-permanent AF	**CR:** **F:** 3 d/week **I:** Vigorous **T:** 40 min/session, 12 weeks **T:** HIIT (Norwegian protocol) in the form of walking or running on a treadmill **S:** 2-3 d/week in-hospital (supervised), 1 d/week choice home-based or in-hospital	HR or RPE: 4x4 min 85-95% HR_{peak}, 3x3 min 60-70% HR_{peak} If in AF, RPE (Borg scale) used instead	**Control:** Advised to continue their usual lifestyle	**$\dot{V}O_{2peak}$** (mL/kg/min): CPET with direct breath-by-breath analysis on a treadmill **QoL:** General QoL (SF-36) **Physical:** Resting systolic and diastolic BP **Measurement timepoints:** Baseline and 3-month follow-up

Melo *et al.*, 2019, Portugal Single-centre RCT ClinicalTrials # NCT02413151	Persistent AF, chronic HF (II-IV) and CRT	**CR:** **F:** 2 d/week **I:** Vigorous **T:** 60 min/session, 6 months **T:** HIIT (Norwegian protocol) **P:** During the first month, each work and recovery bouts were increased by 30s/week **S:** In-hospital (supervised)	HR: 4x4 min 90-95% HR_{peak} (or below device threshold), 3x3 min 60-70% HR_{peak}	**Control:** No specific advice given and did not undergo supervised training	$\dot{V}O_{2peak}$ (mL/kg/min): CPET with direct breath-by-breath analysis on a treadmill **QoL:** HeartQoL **Physical:** Resting systolic and diastolic BP, HR, BMI **Mental:** Anxiety and Depression (HADS) **Adherence:** % sessions attended **Measurement timepoints:** Baseline and 6-month follow-up
Mills *et al.*, 2020, UK Single-centre pre-post study	Symptomatic AF	**CR:** **F:** 2 d/week **T:** 6 weeks **T:** 1 gym- and 1 circuit-based/week + weekly education **S:** In-hospital (supervised)	NR	-	**Physical:** Resting systolic and diastolic BP, HR, BMI, functional capacity (6MWT) **Mental:** Anxiety (GAD-7) and Depression (PHQ-9) **Adherence:** Only those with full adherence were included in the study **Measurement timepoints:** Baseline and 6 weeks
Nguyen *et al.* 2020; De With *et al.*, 2019, RACE 3 study, Netherlands and UK Multi-centre RCT ClinicalTrials # NCT00877643	Persistent AF with mild-to-moderate HF	**INT1: 4 therapies** 1. Mineralocorticoid receptor antagonists 2. Statins 3. ACE-I and/or receptor blockers 4. CR: **F:** 2-3 d/week **I:** Moderate **T:** 35-45 min/session, 9-11 weeks **T:** Aerobic conditioning on a cycle ergometer or treadmill. A nurse counseled participants for behaviour change once every 6 weeks **S:** In-hospital (supervised)	Talk test: able to speak full sentences/ comfortable conversation	**Control:** Usual care (causal treatment of AF and HF, and treated with rhythm control therapy)	**QoL:** AF-specific (AFSS) and General (SF-36) **Physical:** Resting systolic and diastolic BP, HR, BMI **PA levels:** Self-reported (classified as meeting or not ≥150 min/week of moderate PA) **Adherence:** % exercise sessions attended **Measurement timepoints:** Baseline, 3-month and 1-year follow-up
Okazaki *et al.*, 2016, Japan	Subset of patients with	**CR:** **F:** 1-3 d/week **I:** The exercise prescription was individualized	Combination of Wpeak (W at 1 min	**Control:** Outpatient usual care	$\dot{V}O_{2peak}$ (mL/kg/min): CPET with direct breath-by-breath analysis

Single-centre pre-post study	AF and either HF or MI	for each patient, intensity unclear **T:** 60 min/session for 150 days (as per insurance coverage in Japan) **T:** Cycle ergometer + resistance training **S:** In-hospital (supervised)	before the anaerobic threshold), HR or RPE	and nutrition information	
Reed *et al.*, 2022, Canada Single-centre RCT ClinicalTrials # NCT02602457	Persistent and permanent AF	**MICT (INT1):** **F:** 2 d/week **I:** Moderate-to-vigorous **T:** 60 min/session, 12 weeks **T:** Combined continuous aerobic conditioning (30 min) and resistance training (10 min) **S:** In-hospital (supervised) **HIIT (INT2):** **F:** 2 d/week **I:** Vigorous **T:** 23 min/session, 12 weeks **T:** HIIT (16 min: 2 x 8 sets of 30s high-intensity bouts + 30s low-intensity bouts) on a cycle ergometer **P:** PPO may progress to ≤150% **S:** In-hospital (supervised)	HR, RPE or PPO: **INT1:** 67-95% HR_{peak} 12-16 RPE **INT2:** Work: 80-100% of PPO Recovery: 25% of PPO		**$\dot{V}O_{2peak}$** (mL/kg/min): CPET with breath-by-breath direct analysis on a cycle ergometer. **QoL:** AF-specific (AFSS) and General (SF-36) **Physical:** Resting systolic and diastolic BP, HR, BMI, body fat, functional capacity (6MWT) **Mental:** Anxiety and Depression (HADS) **Adherence:** % exercise sessions attended **Measurement timepoints:** Baseline, 3- and 12-month follow-up
Tamulevičiūtė-Prascienė *et al.*, 2022, Lithuania Single-centre RCT ClinicalTrials # NCT04234087	Patients with AF after valve surgery	**CR + balance and resistance training:**** **F:** 2-6 d/week **I:** Moderate **T:** 15-40 min/session, 20-day CR + 12-week maintenance phone calls **T:** Combined aerobic (40 min/session, 6 d/week on a cycle ergometer), stretching (30 min/session, 5 d/week), aerobic endurance (40 min/session, 6 d/week, e.g., marching on spot) ± education. 2-3 d/week: 15-min balance and 25-min resistance training (3 sets, 5-15 reps, 4-6 low limb exercises)	RPE, HR, PPO: Aerobic: 30-50% PPO or 60-70% HR_{peak} Resistance: RPE 11 to ≤15 points, <30% 1 RM to 60% 1 RM		**$\dot{V}O_{2peak}$** (mL/kg/min): CPET on a cycle ergometer with direct breath-by-breath analysis. **QoL:** General QoL (SF-36) **Physical:** Functional capacity (6MWT) **Adherence:** number of exercise sessions attended **Measurement timepoints:** Baseline, 20-day and 3-month follow-up

		P: From low (<30% 1 RM, RPE ≤11, 5-10 reps) to moderate (≤60% 1 RM, RPE 12-13, 8-15 reps) intensity **S:** In-hospital (supervised, group) **Maintenance:** For 12 weeks, they received 6 calls to facilitate the continuation of exercise			
Wagner *et al.*, 2018; Risom *et al.*, 2016 CopenHeartRFA study, Denmark Single-centre RCT ClinicalTrials # NCT01523145	Patients who underwent ablation for AF	**CR:** **F:** 3 d/week **I:** Moderate-to-vigorous **T:** 60 min/session, 12 weeks **T:** Combined aerobic and resistance training + 4 psycho-educational consultations with a nurse **P:** The training intensity increased progressively throughout the program **S:** First session: in-hospital (supervised). Other: choice in-hospital (supervised), community (supervised) or home-based (diary and pulse watch)	RPE and HR: Aerobic: RPE 13-17, 50-80% HR_{peak} Resistance: 30-40% 1RM upper body; 40-50% 1RM lower body	**Control:** Usual care post-ablation involved a consultation with a physician at 3- and 6-months' follow-up	**$\dot{V}O_{2peak}$** (mL/kg/min): CPET with direct breath-by-breath analysis was used, yet $\dot{V}O_{2peak}$ was estimated in 25% of patients: 10.8 x (W_{peak}/weight) + 3.5 **QoL:** AF-specific (AFEQT) and General (SF-36) **Mental:** Anxiety and Depression (HADS) **Adherence:** % sessions attended **Measurement timepoints:** Baseline, 3-, 6- and 12- month follow-up

*Intensity range based on the criteria specified by O'Neill *et al.* 2021 (Table 3) [74]. **Conventional CR (INT2): not included in the review as did not meet the eligibility of ≥4 weeks duration. ACE-I: Angiotensin converting enzyme inhibitors; AF: Atrial fibrillation; AFEQT: Atrial fibrillation effect on quality-of-life; AFSS: University of Toronto atrial fibrillation severity scale; BMI: Body mass index; BP: Blood pressure, C/D: Cool-down, CIED: Cardiac implantable electrical device; CPET: Cardiopulmonary exercise testing; CR: Cardiovascular rehabilitation; CRT: Cardiac resynchronization therapy; GAD: General anxiety disorder; HADS: Hospital anxiety and depression scale; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HIIT: High-intensity interval training; HR: Heart rate; INT: Intervention; IPAQ: International physical activity questionnaire; ISWT: Incremental shuttle walking test; MI: Myocardial infarction; MICT: Moderate- to vigorous-intensity continuous training; MLHFQ: Minnesota living with heart failure questionnaire; PA: Physical activity; PHQ: Patient health questionnaire; PPO: Peak power output; RCT: Randomized clinical trial; RPE; Ratings of perceived exertion; RM: Maximal repetition; SF-36: Short-form-36; 6MWT; Six-minute walk test; $\dot{V}O_{2peak}$: Peak aerobic power; W: Watts (workload); W/U: Warm-up.

Participant characteristics

A total of 1,375 participants were included (see Table 6.2.). Of these, 868 were in an exercise training group (n=254 [29%] females, mean ± SD, F: 69±7, M: 66±8 years old). The proportion of females in each study ranged between 0% and 58% (mean: 27%). Eight studies included participants with non-permanent AF[37,39,61,62,64,65,69,70] and three studies included participants with permanent AF only.[35,60,73] Among studies that reported the type of AF, a total of 64 females and 153 males in an exercise group had paroxysmal AF, 73 females and 198 males had persistent AF, and 52 females and 146 males had permanent AF.

Multiple co-morbidities and CVD risk factors were reported across studies (e.g., hypertension, diabetes, coronary artery disease, valvular disease). Seven studies enrolled patients with heart failure,[60,63,67–70,73] and one study included patients who had experienced acute heart failure or myocardial infarction.[63] The mean baseline BMI across most groups was in the overweight or obese categories, except for two studies.[63,65] Four studies included participants who had recently undergone an ablation[15,61,62,65] and two included patients in cardiac resynchronization therapy.[69,73] Anticoagulants, β-blockers and ACE-inhibitors were amongst the most frequently prescribed medications. Few sociodemographic and gender-related data were reported (n=10 studies). Race/ethnicity data were available from nine studies, of which six, one and two studies included predominantly White,[41,61,64,67,68,73] East Asian[65] and Japanese[62,63] participants, respectively. Four studies reported on the education level (n=2 studies: ~half of participants <5 years of higher education;[15,41] n=1: ~half had a university degree;[61] n=1: <1/4 had a university degree[65]) five on the employment status (n=3: most participants were retired;[14,67,68] n=2: half or more were employed[15,61]), and three on social support (n=3: half or more were living with someone[15,67,68]).

Table 6.2. Participant characteristics of the studies included in the systematic review.

Study	Sex	N (%)	Socio-demographic and gender-related factors	Age, years	BMI, kg/m^2 Body fat %*	AF type, n (%)	Co-morbidities and medical procedures, n (%)	Prescribed medications, n (%)**
Alves *et al.*, 2022	M	26 (100)	NR	INT	INT	INT	INT	INT
				58 (3) n=13	30.0 (2.0)	Permanent: 13 (100)	NYHA I: 6 (46), NYHA II: 7 (54) 100% of the sample had HFrEF***	ACE-I: 13 (100), Amiodarone: 1 (8), Amlodipine: 2 (15), Anti-coagulant: 12 (92), β-blocker: 13 (100), Digoxin: 8 (62), Diuretic: 13 (100), Spironolactone: 9 (69), Statin: 5 (38)
				C	Control	Control	Control	Control
				58 (2) n=13	26.0 (1.0)	Permanent: 13 (100)	NYHA I: 4 (31), NYHA II: 9 (69)	ACE-I: 11 (85), Amiodarone: 1 (8), Amlodipine: 1 (8), Anti-coagulant: 12 (92), β-blocker: 13 (100), Digoxin: 10 (77), Diuretic: 13 (100), Spironolactone: 8 (62), Statin: 6 (46)
Bittman *et al.*, 2022	F	30 (40)	INT	INT	INT	INT	INT	INT
			White: 9 (81)	67 (6) n=13	32.2 (6.6) 44.7 (3.7)%*	NR	CAD: 2 (18), Diabetes: 1 (9), High-risk waist circumference: 9 (82), HTN: 6 (55), OSA: 7 (64)	Amiodarone: 3 (27), β-blocker: 6 (55), Cholesterol Pills: 4 (36), Diabetes Pills: 1 (9), HTN Pills: 7 (64), Other Anti-arrhythmic: 4 (36)
			Control	C	Control	Control	Control	Control
			White: 11 (65)	66 (8) n=17	32.5 (7.4) 44.3 (4.6)%*	NR	CAD: 2 (12), Diabetes: 4 (24), High-risk waist circumference: 14 (82), HTN: 12 (71), OSA: 11 (65)	Amiodarone: 2 (12), β-blocker: 10 (59), Cholesterol Pills: 11 (65), Diabetes Pills: 5 (29), HTN Pills: 11 (65), Other Anti-arrhythmic: 5 (29)
	M	44 (60)	INT	INT	INT	INT	INT	INT
			White: 14 (61)	62 (9) n=22	30.9 (5) 32.2 (4.5)%*	NR	CAD: 3 (13), Diabetes: 4 (17), High-risk waist circumference: 22 (96), HTN: 15 (65), OSA: 17 (74)	Amiodarone: 2 (9), β-blocker: 16 (70), Cholesterol Pills: 17 (74), Diabetes Pills: 3 (13), HTN Pills: 14 (61), Other Anti-arrhythmic: 10 (44)

			Control	C	Control	Control	Control	Control
			White: 11 (52)	57 (9) n=21	30.3 (3.3) 30.1 (2.6)%*	NR	CAD: 4 (19), Diabetes: 4 (19), High-risk waist circumference: 18 (86), HTN: 12 (57), OSA: 16 (76)	β-blocker: 6 (29), Cholesterol Pills: 11 (52), Diabetes Pills: 4 (19), HTN Pills: 13 (62), Other Anti-arrhythmic: 5 (24)
Borland *et al.*, 2020	F	28 (29)	NR	INT 1	INT 1	INT 1	INT 1	INT 1
				73 (4) n=12	29.1 (4.3)	Permanent: 12 (100)	Diabetes: 2 (17), HTN: 3 (25), Previous MI: 1 (8)	Anti-coagulant: 11 (92), Anti-platelet: 1 (8), COPD medication: 1 (8), Diuretic: 3 (25), HR regulator: 8 (67), Insulin: 2 (17)
				INT 2	INT 2	INT 2	INT 2	INT 2
				75 (6) n=16	26.4 (3.8)	Permanent: 16 (100)	Diabetes: 3 (19), HTN: 6 (38), Previous MI: 2 (13)	Anti-coagulant: 14 (88), Anti-platelet: 1 (6), CCB: 3 (19), COPD medication: 1 (6), Diuretic: 4 (25), HR regulator: 16 (100), Insulin: 2 (13)
	M	68 (71)	NR	INT 1	INT 1	INT 1	INT 1	INT 1
				75 (4) n=34	28.4 (4.3)	Permanent: 34 (100)	COPD: 1 (3), Diabetes: 1 (3), HTN: 10 (29), Previous MI: 1 (3), Valve surgery: 2 (6)	Anti-coagulant: 33 (97), Anti-platelet: 2 (6), CCB: 4 (12), COPD medication: 2 (24), Diuretic: 8 (24), HR regulator: 29 (85), Insulin: 1 (3)
				INT 2	INT 2	INT 2	INT 2	INT 2
				73 (6) n=34	28.5 (4.6)	Permanent: 34 (100)	Diabetes: 2 (6), HTN: 9 (27), Valve surgery: 2 (6)	Anti-coagulant: 30 (88), Anti-platelet: 2 (6), CCB: 7 (21), Diuretic: 7 (21), HR regulator 26 (77), Insulin: 2 (6)
Cai *et al.*, 2022	F	34 (34)	INT 1	INT 1	INT 1	INT 1	INT 1	INT 1
			Completed University: 5 (28) 100% East Asian***	59 (12) n=18	24.8 (2.6)	Paroxysmal: 12 (67) Persistent: 6 (33)	CAD: 3 (17), Diabetes: 2 (11), HTN: 18 (44), NYHA II-IV: 14 (78) 100% had undergone ablation***	NR

			INT 2	INT 2	INT 2	INT 2	INT 2	INT 2
			Completed University: 2 (13)	60 (9) n=16	25.4 (3.6)	Paroxysmal: 11 (69) Persistent: 5 (31)	CAD: 1 (6), Diabetes: 2 (13), HTN: 10 (63), NYHA II-IV: 15 (59)	NR
	M	66 (66)	INT 1	INT 1	INT 1	INT 1	INT 1	INT 1
			Completed University: 4 (13)	57 (11) n=32	24.4 (4.3)	Paroxysmal: 23 (72) Persistent: 9 (28)	CAD: 4 (13), Diabetes: 4 (13), HTN: 15 (47), NYHA II-IV: 19 (78)	NR
			INT 2	INT 2	INT 2	INT 2	INT 2	INT 2
			Completed University: 6 (18)	55 (9) n=34	32.4 (7.4)	Paroxysmal: 17 (50) Persistent: 17 (50)	CAD: 4 (12), Diabetes: 5 (6), HTN: 17 (50), NYHA II-IV: 18 (53)	NR
Dabrowski *et al.*, 2018	F	3 (6)	100% White***	INT	INT	INT	INT	INT
				58 n=1	51.0	Permanent: 1 (100)	CVD: 1 (100), Smoker: 1 (100); 100% had CIED (CRT-D or ICD) and HFrEF (NYHA III)***	ACE-I: 1 (100), ASA: 1 (100), β-blocker: 1 (100), Diuretic: 1 (100), Potassium: 1 (100), Statin: 1 (100)
				C	Control	Control	Control	Control
				59 (4) n=2	84.0 (8.5)	Permanent: 2 (100)	CVD: 2 (100), Diabetes: 2 (100), Dyslipidemia: 1 (50), HTN: 1 (50), OSA: 1 (50), Smoker: 1 (50)	ACE-I: 2 (100), Anti-coagulant: 2 (100), Anti-diabetic: 1 (50), β-blocker: 2 (100), CCB: 1 (50), Clopidogrel: 1 (50), Digoxin: 1 (50), Diuretic: 2 (100), Insulin: 2 (100), Statin: 1 (50)
	M	46		INT	INT	INT	INT	INT

		(94)		64 (9) n=21	87.9 (14.7)	Permanent: 21 (100)	CVD: 12 (57), Diabetes: 7 (33), Dyslipidemia: 12 (57), HTN: 9 (43), OSA: 2 (10), Smoker: 9 (45)	ACE-I: 19 (90), Anti-coagulant: 15 (71), Anti-diabetic: 4 (19), ARB: 3 (14), ASA: 11 (52), β-blocker: 21 (100), CCB: 1 (5), Clopidogrel: 4 (19), Digoxin: 9 (43), Diuretic: 21 (100), Fibrates: 1 (5), Insulin: 1 (5), Potassium: 8 (38), Statin: 14 (67)
				C	Control	Control	Control	Control
				67 (7) n=25	87.4 (18.7)	Permanent: 25 (100)	CVD: 15 (60), Diabetes: 11 (44), Dyslipidemia: 15 (63), HTN: 12 (48), OSA: 1 (4), Smoker: 10 (40)	ACE-I: 21 (84), Anti-coagulant: 20 (80), Anti-diabetic: 4 (16), ARB: 4 (16), ASA: 7 (28), β-blocker: 25 (100), CCB: 2 (8), Clopidogrel: 3 (12), Digoxin: 9 (36), Diuretic: 20 (80), Fibrates: 1 (4), Insulin: 5 (20), Potassium: 12 (48), Statin: 18 (72)
Dalal *et al.*, 2019	F	16 (15)	INT	INT	INT	INT	INT	INT
			Living with a partner: 4 (50) Retired: 8 (100) White: 7 (88)	76 (9) n=8	25.9 (4.1)	NR	CAD: 3 (38), Diabetes: 1 (13), HTN: 2 (25), Valve disease: 1 (13); 100% of the sample had HFrEF***	ACE-I: 3 (38), Aldosterone-receptor-antagonist: 5 (63), Anti-coagulant: 6 (75), ARB: 2 (25), β-blocker: 6 (75), Loop-Diuretic: 6 (75), Nitrate: 2 (25)
			Control	C	Control	Control	Control	Control
			Living with a partner: 3 (83) Retired: 8 (100) White: 8 (100)	79 (5) n=8	26.7 (6.9)	NR	CAD: 3 (38), COPD: 1 (13), Diabetes: 1 (13), HTN: 5 (63), Smoker: 1 (13), Valve disease: 3 (38)	ACE-I: 3 (38), Aldosterone-receptor-antagonist: 5 (63), Anti-coagulant: 6 (75), ARB: 5 (63), β-blocker: 8 (100), Digoxin: 4 (50), Loop-Diuretic: 6 (75), Nitrate: 2 (25)
	M	92	INT	INT	INT	INT	INT	INT

		(85)	Living with a partner: 36 (69) Retired: 43 (83) White: 51 (98)	72 (10) n=52	30.3 (7.6)	NR	CAD: 19 (37), COPD: 5 (10), Diabetes: 16 (31), HTN: 22 (42), Smoker: 4 (8), Valve disease: 13 (25)	ACE-I: 38 (73), Aldosterone-receptor-antagonist: 27 (52), Anti-coagulant: 40 (77), ARB: 10 (19), β-blocker: 45 (87), Digoxin: 13 (25), Loop-Diuretic: 35 (67), Nitrate: 7 (13), Thiazide-Diuretic: 2 (4)
			Control	C	Control	Control	Control	Control
			Living with a partner: 34 (85) Retired: 33 (83) White: 38 (95)	71 (10) n=40	30.2 (6.6)	NR	CAD: 14 (35), COPD: 5 (13), Diabetes: 6 (15), HTN: 14 (35), Smoker: 1 (3), Valve disease: 11 (28)	ACE-I: 28 (70), Aldosterone-receptor-antagonist: 24 (60), Anti-coagulant: 33 (83), ARB: 8 (20), β-blocker: 33 (83), Digoxin: 11 (28), Loop-Diuretic: 31 (78), Nitrate: 5 (13)
Joensen *et al.*, 2019	F	18 (35)	NR	INT	INT	INT	INT	INT
				67 (7) n=11	28.4 (6.6)	Paroxysmal: 9 (82) Persistent: 2 (18)	COPD: 2 (18), HTN: 5 (46), Obesity: 6 (67), OSA: 1 (9)	ACE-I: 1 (9), ARB: 2 (18), β-blocker: 8 (80), Dabigatran (Anti-coagulant): 1 (9), Statin: 3 (27), Warfarin: 3 (27),
				C	Control	Control	Control	Control
				66 (6) n=7	29.5 (5.7)	Paroxysmal: 4 (57) Persistent: 3 (43)	COPD: 1 (14), HTN: 4 (47), Obesity: 7 (100)	ACE-I: 1 (14), Amiodarone: 1 (14), β-blocker: 6 (86), Dabigatran (Anti-coagulant): 1 (14), Magnyl (NSAIDs): 2 (29), Statin: 2 (29), Warfarin: 3 (43)
	M	34 (65)	NR	INT	INT	INT	INT	INT
				59 (11) n=17	27.5 (4.0)	Paroxysmal: 7 (44) Persistent: 9 (56)	HTN: 7 (41), Obesity: 12 (75), OSA: 1 (6), Smoker: 1 (6)	ACE-I: 5 (29), Amiodarone: 3 (18), ARB: 3 (18), β-blocker: 10 (59), Dabigatran (Anti-coagulant): 1 (6), Flecainide: 3 (18), Magnyl (NSAIDs): 2 (12), Warfarin: 8 (47), Statin: 5(29)
				C	Control	Control	Control	Control

				58 (9) n=17	27.2 (3.1)	Paroxysmal: 5 (36) Persistent: 9 (64)	HTN: 5 (29), Obesity: 13 (76), Smoker: 1 (6)	ACE-I: 1 (6), Amiodarone: 1 (6), ARB: 1 (6), β-blocker: 10 (59), Dabigatran (Anti-coagulant): 2 (12), Flecainide: 4 (24), Warfarin: 8 (47), Statin: 3 (18)
Kato *et al.*, 2019	F	11 (19)	100% of the sample was Japanese***	INT	INT	INT	INT	INT
				70 (13) n=8	NR	Persistent: 8 (100)	HF: 4 (50), HTN: 6 (75), Obesity: 1 (12)	NR
				C	Control	Control	Control	Control
				72 (10) n=3	NR	Persistent: 3 (100)	HTN: 3 (100)	NR
	M	48 (81)		INT	INT	INT	INT	INT
				65 (10) n=20	NR	Persistent: 20 (100)	CAD: 1 (5), Diabetes: 5 (25), HF: 2 (10), HTN: 12 (60), Obesity: 7 (35), Smoker: 6 (30)	NR
				C	Control	Control	Control	Control
				63 (9) n=28	NR	Persistent: 28 (100)	CAD: 3 (10), COPD: 2 (7), Diabetes: 6 (21), HF: 4 (14), HTN: 16 (57), Obesity: 9 (32), Smoker: 2 (7)	NR
Lang *et al.*, 2018	F	10 (53)	INT	INT	INT	INT	INT	INT
			Retired: 6 (100) White: 6 (100)	80 (5) n=6	32.4 (3.0)	NR	COPD: 1 (17), Diabetes: 2 (33), HTN: 5 (83), Valve disease: 1 (17); 100% HFpEF***	ACE-I: 4 (67), Aldosterone-receptor-antagonist: 2 (33), Anti-coagulant: 4 (67), ARB: 1 (17), β-blocker: 1 (17), Digoxin: 1 (17), Loop-Diuretic: 6 (100), Nitrate: 2 (33)

			Control	C	Control	Control	Control	Control
			Living with a partner: 2 (50) Retired: 4 (100) White: 4 (100)	80 (4) n=4	29.4 (4.5)	NR	Diabetes: 1 (25), HTN: 2 (50), Valve disease: 1 (25)	ACE-I: 1 (25), Anti-coagulant: 3 (75), β-blocker: 4 (100), Digoxin: 1 (25), Loop-Diuretic: 3 (75)
	M	9 (47)	INT	INT	INT	INT	INT	INT
			Living with a partner: 6 (86) Retired: 7 (100) White: 7 (100)	72 (5), n=7	32.4 (5.1)	NR	CAD: 2 (29), COPD: 2 (29), Diabetes: 2 (29), HTN: 4 (57), Smoker: 1 (14), Valve disease: 1 (14)	ACE-I: 2 (29), Aldosterone-receptor-antagonist: 2 (29), Anti-coagulant: 7 (100), ARB: 3 (43), β-blocker: 4 (57), Digoxin: 2 (29), Loop-Diuretic: 6 (86), Thiazide-Diuretic: 1 (14)
			Control	C	Control	Control	Control	Control
			Living with a partner: 1 (50) Retired: 1 (50) White: 2 (100)	65 (13) n=2	31.1 (6.9)	NR	COPD: 1 (50), HTN: 2 (100), Smoker: 1 (50), Valve disease: 1 (50)	Aldosterone-receptor-antagonist: 1 (50), Anti-coagulant: 2 (100), ARB: 1 (50), β-blocker: 2 (100), Digoxin: 1 (50), Loop-Diuretic: 2 (100), Nitrate: 1 (50)
Makhinova *et al.*, 2017	M	48 (100)	INT	INT	INT	INT	INT	INT
			Employed: 13 (54) University degree: 12 (50) White: 24 (100)	57 (8) n=24	28.4 (3.0)	Paroxysmal: 24 (100)	CAD: 1 (4), HF: 1 (4), HTN: 24 (50), Obesity: 8 (33), Smoker: 1 (4)	β-blocker
			Control	C	Control	Control	Control	Control
			Employed: 16 (67)	55 (10) n=24	28.2 (3.8)	Paroxysmal: 24 (100)	CAD: 1 (4), HF: 1 (4), HTN: 24 (50), Obesity: 7 (29), Smoker: 3 (13),	β-blocker

			University degree: 12 (50) White: 24 (100)					
Malmo *et al.*, 2016	F	9 (18)	NR	INT	INT	INT	INT	INT
				60 (9) n=6	85.6 (22.0)	Paroxysmal: 5 (83) Persistent: 1 (17)	CAD: 1 (17), Diabetes: 1 (17), HTN: 4 (67)	NR
				C	Control	Control	Control	Control
				62 (15) n=3	84.4 (14.2)	Paroxysmal: 3 (100)	HTN: 24 (50)	NR
	M	42 (82)	NR	INT	INT	INT	INT	INT
				55 (7) n=20	93.2 (13.2)	Paroxysmal: 10 (50) Persistent: 10 (50)	Diabetes: 1 (5), HTN: 1 (33), Smoker: 1 (6)	NR
				C	Control	Control	Control	Control
				62 (9) n=22	95.0 (17.2)	Paroxysmal: 11 (50) Persistent: 11 (50)	CAD: 2 (9), Diabetes: 1 (5), HTN: 7 (32)	NR
Melo *et al.*, 2019	F	4 (21)	NR	INT	INT	INT	INT	INT
				67 (0) n=2		Persistent: 2 (100)	CAD: 1 (50), Dyslipidemia: 1 (50), HTN: 2 (100)	ACE-I or ARB: 2 (100), Anti-coagulant: 2 (100), β-blocker: 1 (50), Diuretic: 2 (100)
				C	Control	Control	Control	Control

				63 (13) n=2		Persistent: 2 (100)	CAD: 1 (50), Diabetes: 1 (100), Dyslipidemia: 1 (50), HTN: 1 (50), Obesity: 1 (50)	ACE-I or ARB: 1 (100), Anti-coagulant: 1 (100), Anti-diabetic: 1 (100), β-blocker: 1 (100)
	M	15 (79)	NR	INT	INT	INT	INT	INT
				73 (3) n=6		Persistent: 6 (100)	CAD: 2 (67), Diabetes: 2 (50), Dyslipidemia: 4 (57), HTN: 4 (100), Obesity: 2 (50)	ACE-I or ARB: 5 (100), Anti-coagulant: 4 (80), Anti-diabetic: 1 (33), β-blocker: 4 (100), Diuretic: 5 (100)
				C	Control	Control	Control	Control
				69 (9) n=9		Persistent: 9 (100)	CAD: 2 (40), Diabetes: 4 (50), Dyslipidemia: 4 (100), HTN: 7 (88), Obesity: 3 (38)	ACE-I or ARB: 7(100), Anti-coagulant: 6 (86), β-blocker: 6 (100), Anti-diabetic: 1 (25), Diuretic: 7 (100)
Mills *et al.*, 2020	F	19 (58)	NR	INT	INT	INT	INT	INT
				65 (9) n=19	91.2 (24.0)	Paroxysmal: 9 (47) Persistent: 9 (47) Permanent: 1 (6)	CAD: 3 (16), Diabetes: 3 (16), Dyslipidemia: 10 (53), HF: 2 (11), HTN: 11 (58), Obesity: 14 (74), OSA: 2 (11), Physically inactive: 19 (100), Valve disease: 1 (5)	Anti-arrhythmic: 10 (53), β-blocker: 16 (84)
	M	14 (42)	NR	INT	INT	INT	INT	INT
				62 (11) n=14	113.1 (20.6)	Paroxysmal: 6 (43) Persistent: 7 (50)	CAD: 2 (14), Diabetes: 2 (14), Dyslipidemia: 10 (53), HF: 3 (21), HTN: 9 (64), Obesity: 11 (79), OSA: 2	Anti-arrhythmic: 4 (29), β-blocker: 11 (79)

						Permanent: 1 (7)	(14), Physically inactive: 14 (100)	
Nguyen *et al.*, 2020	F	52 (21)	NR	INT	INT	INT	INT	INT
				66 (8) n=25	30.2 (4.8)	Persistent: 25 (100)	CAD: 5 (20), COPD: 3 (12), Diabetes: 3 (12), HF: 25 (100), HTN: 17 (63), Obesity: 15 (60), Smoker: 2 (8)	ACE-I: 7 (28), Anti-coagulant: 24 (96), ARB: 7 (28), β-blocker: 23 (92), Digoxin: 9 (36), Diuretic: 14 (56), Statin: 10 (40)
				C	Control	Control	Control	Control
				69 (8) n=27	29.6 (5.0)	Persistent: 27 (100)	CAD: 1 (4), COPD: 2 (7), Diabetes: 3 (11), HF: 27 (100), HTN: 15 (60), Obesity: 14 (52), Smoker: 1 (4)	ACE-I: 13 (48), Anti-coagulant: 27 (100), ARB: 4 (15), β-blocker: 24 (89), Digoxin: 9 (33), Diuretic: 14 (52), Statin: 6 (22), Verapamil/diltiazem: 3 (11)
	M	193 (79)	NR	INT	INT	INT	INT	INT
				64 (9) n=94	28.5 (3.5)	Persistent: 94 (100)	CAD: 14 (15), COPD: 6 (6), Diabetes: 7 (7), HF: 94 (100), HTN: 51 (54), Obesity: 39 (42), Smoker: 8 (9)	ACE-I: 31 (33), Aldosterone-receptor-antagonist: 1 (1), Anti-coagulant: 92 (98), ARB: 17 (18), β-blocker: 79 (84), Digoxin: 23 (25), Diuretic: 37 (39), Statin: 30(32), Verapamil/diltiazem: 3 (3)
				C	Control	Control	Control	Control
				65 (9) n=99	28.5 (4.2)	Persistent: 99 (100)	CAD: 13 (13), COPD: 9 (9), Diabetes: 13 (13), HF: 99 (100), HTN: 61 (62), Obesity: 42 (43), Smoker: 16 (16)	ACE-I: 35 (36), Aldosterone-receptor-antagonist: 3 (3), Anti-coagulant: 97 (99), ARB: 24 (25), β-blocker: 84 (86), Digoxin: 23 (24), Diuretic: 34 (35), Statin: 36(37), Verapamil/diltiazem: 8 (8)

Okazaki *et al.*, 2016	F	12 (29)	100% Japanese***	INT	INT	INT	INT	INT
				68 (10) n=7	21.9 (3.2)	NR	CAD: 1 (14), COPD: 1 (14), Diabetes: 2 (29), Dyslipidemia: 5 (71), HTN: 4 (57), Valve disease: 5 (71)	ACE-I or ARB: 5 (71), Anti-diabetic: 2 (29), β-blocker: 7 (100), CCB: 2 (29), Diuretic: 7 (100), Statin: 5 (71)
				C	Control	Control	Control	Control
				66 (13) n=5	22.0 (3.1)	NR	Diabetes: 2 (40), Dyslipidemia: 2 (40), HTN: 3 (60), Valve disease: 2 (40)	ACE-I or ARB: 2 (40), CCB: 2 (40), β-blocker: 4 (80), Diuretic: 5 (100), Statin: 1 (20)
	M	30 (71)		INT	INT	INT	INT	INT
				71 (8) n=6	24.6 (4.1)	NR	CAD: 3 (50), COPD: 1 (17), Diabetes: 6 (100), Dyslipidemia: 2 (33), HTN: 2 (33), Valve disease: 2 (33)	ACE-I or ARB: 5 (83), Anti-diabetic: 6 (100), CCB: 4 (67), β-blocker: 5 (83), Diuretic: 4 (67), Statin: 3 (50)
				C	Control	Control	Control	Control
				66 (9) n=24	23.5 (4.0)	NR	CAD: 7 (29), COPD: 2 (8), Diabetes: 10 (42), Dyslipidemia: 9 (38), HTN: 14 (58), Valve disease: 7 (29)	ACE-I or ARB: 21 (88), Anti-diabetic: 5 (21), CCB: 3 (13), β-blocker: 23 (96), Diuretic: 22 (92), Statin: 8 (33)
Reed *et al.*, 2022	F	28 (33)	INT 1	INT 1	INT 1	INT 1	INT 1	INT 1
			<5y of higher education: 5 (45) Retired: 9 (82) White: 10 (91)	74 (10) n=14	28.6 (8.4)	Persistent: 8 (57) Permanent: 6 (43)	CAD: 1 (7), Diabetes: 2 (14), Dyslipidemia: 2 (14), HF: 2 (14), HTN: 7 (50)	ACE-I: 2 (14), Anti-arrhythmic: 1 (7), Anti-coagulant: 13 (93), Anti-diabetic: 1 (7), Anti-platelet: 1 (7), ARB: 5 (36), β-blocker: 6 (43), CCB: 5 (36), Digoxin: 1 (7), Diuretic: 2 (14), Nitrate: 1 (7), Statin: 3 (21), Thyroid: 5 (36)

			INT 2	INT 2	INT 2	INT 2	INT 2	INT 2
			<5y of higher education: 3 (27) Retired: 8 (73) White: 10 (91)	68 (8) n=14	32.0 (6.3)	Persistent: 5 (36) Permanent: 9 (64)	Diabetes: 1 (7), Dyslipidemia: 3 (21), HTN: 8 (57), OSA: 1 (7), Valve disease: 1 (7)	ACE-I: 2 (14), Anti-arrhythmic 1 (7), Anti-coagulant: 13 (93), Anti-diabetic: 1 (7), Anti-platelet: 1 (7), ARB: 1 (7), β-blocker: 10 (71), CCB: 3 (21), Digoxin: 4 (29), Diuretic: 4 (29), HRT: 1 (7), Statin: 3 (21), Thyroid: 1 (7)
	M	58 (67)	INT 1	INT 1	INT 1	INT 1	INT 1	INT 1
			<5y of higher education: 12 (60) Retired: 15 (75) White: 19 (95)	70 (7) n=29	30.5 (4.8)	Persistent: 9 (31) Permanent: 20 (69)	CAD: 4 (14), COPD: 3 (10), Diabetes: 3 (10), Dyslipidemia: 12 (41), HF: 3 (10), HTN: 16 (55), OSA: 4 (14), Smoker: 1 (3), Valve disease: 1 (3)	ACE-I: 6 (21), Anti-arrhythmic: 3 (10), Anti-coagulant: 25 (86), Anti-depressant: 3 (10), Anti-diabetic: 3 (10), Anti-platelet: 2 (7), ARB: 6 (21), β-blocker: 20 (69), CCB: 4 (14), Digoxin: 4 (14), Diuretic: 8 (28), Nitrate: 3 (10), Statin: 17 (59), Thyroid: 3 (10)
			INT 2	INT 2	INT 2	INT 2	INT 2	INT 2
			<5y of higher education: 10 (50) Retired: 13 (65) White: 17 (85)	69 (8) n=29	30.4 (5.5)	Persistent: 12 (41) Permanent: 17 (59)	CAD: 7 (24), Diabetes: 4 (14), Dyslipidemia: 9 (31), HF: 2 (7), HTN: 17 (59), OSA: 4 (14), Smoker: 1 (3), Valve disease: 1 (3)	ACE-I: 11 (38), Anti-coagulant: 25 (86), Anti-depressant: 2 (7), Anti-diabetic: 1 (3), Anti-platelet: 7 (24), ARB: 5 (17), β-blocker: 19 (66), CCB: 12 (41), Digoxin: 3 (10), Diuretic: 7 (24), Nitrate: 5 (17), Statin: 14 (48), Thyroid: 3 (10)
Tamulevičiūtė Prascienė *et al.*, 2022	F	27 (47)	NR	INT	INT	INT	INT	INT
				78 (6) n=12	28.2 (4.6)	Paroxysmal: 5 (42) Permanent: 7 (58)	Diabetes: 2 (17), HF: 11 (92), HTN: 10 (83), Valve disease: 3 (25)	ACE-I: 8 (67), Anti-platelet: 3 (25), ARB: 2 (17), β-blocker: 11 (92), Diuretic: 10 (83), Orally treated Diabetes: 2 (17), Statin: 4 (33), Warfarin: 11 (92)
	M	31	NR	INT	INT	INT	INT	INT

		(53.4)		73 (6) n=15	26.6 (3.3)	Paroxysmal: 9 (60) Permanent: 6 (40)	Diabetes: 2 (13), HF: 8 (53), HTN: 14 (93), Valve disease: 12 (80)	ACE-I: 10 (67), Anti-platelet: 7 (47), β-blocker: 14 (93), ARB: 2 (13), Diuretic: 14 (93), Orally treated Diabetes: 1 (7), Statin: 11 (73), Warfarin: 14 (93)
Wagner *et al.*, 2018	F	59 (28)	INT	INT	INT	INT	INT	INT
			<5y of higher education: 13 (42) Employed: 12 (39) Living with a partner: 20 (65)	**** 62 (48-77) n=31	NR	Paroxysmal: 24 (77) Persistent: 7 (23)	CAD: 3 (10), Diabetes: 1 (3), NYHA I-II: 24 (80); NYHA III-IV: 6 (20), HTN: 9 (29), Obesity: 5 (16)	ACE-I: 2 (6), Amiodarone: 5 (16), CCB: 7 (23), Digoxin: 2 (6), Warfarin: 28 (90)
			Control	C	Control	Control	Control	Control
			<5y of higher education: 17 (61) Employed: 13 (46) Living with a partner: 18 (64)	63 (24-80) n=28	NR	Paroxysmal: 22 (79) Persistent: 6 (21)	Diabetes: 2 (5), NYHA I-II: 21 (75); NYHA III-IV: 7 (25), HTN: 11 (39), Obesity: 6 (21)	ACE-I: 7 (25), Amiodarone: 4 (14), Anti-coagulant: 1 (4), CCB: 9 (32), Digoxin: 3 (11), Warfarin: 22 (79)
	M	151 (72)	INT	INT	INT	INT	INT	INT
			<5y of higher education: 34 (45) Employed: 41 (55) Living with a partner: 65 (87)	60 (33-75) n=74	NR	Paroxysmal: 52 (70) Persistent: 22 (30)	CAD: 10 (13), Diabetes: 3 (4), NYHA I-II: 68 (92); NYHA III-IV: 6 (8), HTN: 21 (28), Obesity: 13 (18)	ACE-I: 12 (16), Amiodarone: 15 (20), Anti-coagulant: 3 (4), CCB: 15 (26), Digoxin: 9 (12), Warfarin: 64 (86)

Control	C	Control	Control	Control	Control
<5y of higher education: 31 (40) Employed: 44 (62) Living with a partner: 64 (83)	59 (26-79) n=77	NR	Paroxysmal: 54 (70) Persistent: 23 (30)	CAD: 3 (3.9), Diabetes: 3 (4), NYHA I-II: 66 (86); NYHA III-IV: 11 (14), HTN: 20 (26), Obesity: 9 (12)	ACE-I: 11 (14), Amiodarone: 8 (10), Anti-coagulant: 2 (3), CCB: 19 (25), Digoxin: 4 (5), Warfarin: 72 (94)

*Body fat (%); **Medication names reported as described in each study; ***Characteristic present in all participants of the study; **** Age reported as median (interquartile range); ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; ASA: Acetylsalicylic acid; CAD: Coronary artery disease; CCB: Calcium channel blockers; CIED: Cardiovascular implantable electronic device; COPD: Chronic obstructive pulmonary disorder; CRT-D: Cardiac resynchronization therapy defibrillator; CVD: Cardiovascular disease; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HR: Heart rate; HRT: Hormone replacement therapy; Hypertension: HTN; ICD: Implantable cardioverter-defibrillator; INT: intervention (see Table 6.1); MI: myocardial infarction; MRA: Mineralocorticoid Receptor Antagonists; NR: not reported; NSAIDs: Nonsteroidal anti-inflammatory drugs; NYHA I: New York Heart Association Class I; NYHA II: New York Heart Association Class II; NYHA III: New York Heart Association Class III; NYHA IV: New York Heart Association Class IV; OSA: Obstructive sleep apnea.

Risk of bias, quality of the evidence and publication bias

The risk of bias was assessed in 15 RCTs (see Table 6.3.). Two studies without a full text and a study with a pre-post design were not assessed. The mean score was 10.5 of the 15 points. Five studies had a high risk of bias with a score <10 points. More than half of the studies did not appropriately report on allocation concealment and did not conduct intention-to-treat analyses. Only five studies measured and reported the physical activity levels of the control group.[35,37,41,65,72] Few (n=5) studies described how the relative exercise intensity was maintained constant during the program.[15,41,60,64,72] The results from the GRADE approach are summarized in Table 6.4. Overall, the quality of the evidence was low-to-very low. Indirectness was rated as serious given the predominantly male representation in the studies, resulting in a downgrade of the quality across all outcomes. Publication bias was not used to downgrade the quality of the evidence as ≥10 studies per outcome are needed for accurate interpretation of funnel plots.[75] The funnel plots for the most relevant outcomes are presented in Appendix 6.3. for reference. The Egger's test of diastolic blood pressure suggested the presence of publication bias (p=0.06). No other Egger's test revealed publication bias (all p>0.10).

Table 6.3. Assessment of study quality and reporting of randomized controlled trials included in the systematic review.

Studies	STUDY QUALITY					STUDY REPORTING							
	Eligibility specified	Randomi-zation specified	Allocation concealed	Groups similar baseline	Assessor blinded	Measures in >85% participants*	Intention to treat analysis	Between group comparison **	Point measures and variability	Physical activity monitored in control	Relative intensity constant	Exercise prescription specified ***	Total /15 points
Alves	1	1	0	1	1	1	0	2	1	0	1	1	**10**
Bittman	1	1	1	1	1	0	0	2	1	0	1	0	**9**
Borland	1	1	1	1	1	3	1	2	1	1	0	1	**14**
Cai	1	1	0	1	1	3	0	2	1	1	0	0	**11**
Dabrowski	1	0	0	1	0	0	0	2	1	0	0	1	**6**
Dalal	1	1	1	1	1	2	1	2	1	0	0	0	**11**
Joensen	1	1	0	1	1	3	0	2	1	0	0	1	**11**
Kato	1	1	0	1	0	2	0	2	1	0	0	1	**9**
Lang	1	1	1	0	1	2	1	2	0	0	0	0	**9**
Malmo	1	0	0	1	1	3	0	2	1	1	0	1	**11**
Melo	1	1	0	1	0	1	0	2	1	0	0	1	**8**
Nguyen	1	1	0	1	1	2	1	2	1	0	0	0	**10**
Reed	1	1	1	1	1	2	1	2	1	1	1	1	**14**
T.Prasciene	1	1	0	1	1	1	1	2	1	1	1	1	**12**
Wagner	1	1	1	1	1	3	1	2	1	0	1	0	**13**
Total	15	13	6	14	12	28	7	30	14	5	5	9	**Mean 10.5**

*Three points possible: 1 if adherence >85%, 1 if adverse events reported, 1 if exercise attendance reported. **Two points possible: 1 if primary outcome is reported, 1 if all other outcomes are reported. ***The authors did not consider whether the energy expenditure could be calculated. Measured using the tool for the assessment of study quality and reporting in exercise (TESTEX) scale. Only randomized controlled trials with full manuscripts available were assessed.

Table 6.4. Grading of Recommendations Assessment, Development and Evaluation (GRADE) of the most relevant outcomes of the review.

Certainty assessment						№ of patients		Effect (change in Females vs. Males)	Certainty
№ of studies	**Study design (a)**	**Risk of bias (b)**	**Inconsistency (c)**	**Indirectness (d)**	**Imprecision (e)**	**Females**	**Males**	**MD (95% confidence interval)**	
Peak aerobic power (follow up range: 12 weeks to 1 year; assessed with directly measured $\dot{V}O_{2peak}$ in 7 studies and estimated $\dot{V}O_{2peak}$ in 2 studies)									
9	8 randomised trials, 1 pre post	Not serious, borderline	not serious	serious	serious	111 (33%)	221	**MD 0.22 mL O_2/kg/min higher** (1.13 lower to 1.57 higher)	⊕◯◯◯ VERY LOW
General QoL, Short Form-36 (follow up range: 4 weeks to 1 year)									
8	7 randomised trials	Not serious, borderline	not serious	serious	Not serious, borderline	155 (30%)	367	**PCS: MD 0.66 points higher** (1.70 lower to 3.01 higher) **MCS: MD 1.08 points higher** (1.46 lower to 3.62 higher)	⊕⊕◯◯ LOW
Six-minute walk test (follow up range: 6 weeks to 6 months)									
7	6 randomised trials, 1 pre post	Not serious, borderline	serious	serious	serious	134 (36%)	242	**MD 7.11 metres lower** (22.56 lower to 8.34 higher)	⊕◯◯◯ VERY LOW
Resting heart rate (follow up range: 6 weeks to 6 months)									
7	6 randomised trials, 1 pre post	Not serious, borderline	Not serious, borderline	serious	Not serious, borderline	146 (31%)	321	**MD 1.11 bpm higher** (1.42 lower to 3.64 higher)	⊕◯◯◯ VERY LOW
Resting systolic blood pressure (follow up range: 6 weeks to 1 year)									

11	10 randomised trials, 1 pre post	Not serious, borderline	Not serious, borderline	serious	Not serious, borderline	162 (31%)	362	**MD 3.11 mmHg lower** (6.09 lower to 0.14 higher)	⊕◯◯◯ VERY LOW
Resting diastolic blood pressure (follow up range: 6 weeks to 1 year)									
11	10 randomised trials, 1 pre post	Not serious, borderline	serious	serious	Not serious, borderline	162 (31%)	364	**MD 1.79 mmHg lower** (3.77 lower to 0.18 higher)	⊕◯◯◯ VERY LOW
Body bass index (follow up range: 6 weeks to 1 year)									
8	6 randomised trials, 2 pre post	Not serious, borderline	not serious	serious	Not serious, borderline	155 (32%)	332	**MD 0.13 kg/m^2 higher** (0.68 lower to 0.94 higher)	⊕⊕◯◯ LOW
Anxiety, Hospital Anxiety and Depression Scale (follow up range: 12 weeks to 6 months)									
6	5 randomised trials	Not serious, borderline	not serious	serious	Not serious, borderline	60 (27%)	161	**MD 0.22 points lower** (1.77 lower to 1.33 higher)	⊕⊕◯◯ LOW
Depression, Hospital Anxiety and Depression Scale (follow up range: 12 weeks to 6 months)									
6	5 randomised trials	Not serious, borderline	serious	serious	Not serious, borderline	60 (27%)	161	**MD 0.01 points higher** (1.63 lower to 1.64 higher)	⊕◯◯◯ VERY LOW

MD: Mean difference. Explanations: (a) Since most studies were RCTs, the quality of the evidence was initially assigned as “high”.
(b) “Not serious" if none of the studies had a high risk of bias; "Not serious, borderline" if >1 study had a high risk of bias, but this did not represent ≥50% of the studies; “serious” if >1 study had a high risk of bias and they represented ≥50% of the studies. (c) "Not serious" if the heterogeneity was not significant (p>0.05), "not serious, borderline", if heterogeneity was significant with I^2 ≤50%, "serious" if heterogeneity was significant with I^2 >50%. (d) The majority of the research was conducted in males (29% females, 71% males). (e) Wide confidence intervals downgraded the quality of evidence: "serious" indicated that most confidence intervals for the outcome were wide, "not serious, borderline" indicated that some confidence intervals for the outcome were wide. Publication bias was not assessed as none of the outcomes was reported by at least 10 studies.

Primary outcome: Sex differences in $\dot{V}O_{2peak}$ changes following exercise training

The meta-analysis for comparing sex differences in $\dot{V}O_{2peak}$ changes was conducted by pooling data from eleven exercise interventions of eight studies.[15,37,39,62–65,72] Two studies with less than two female participants in the exercise group[69,73] and two which recruited only males[60,61] were excluded. A total of 331 participants were included (n=111, 33% females; n=221 males; see Figure 6.2.), no sex differences were identified for changes in $\dot{V}O_{2peak}$ following exercise training (MD=+0.22, 95% CI -1.13 to +1.57 mL O_2/kg/min, p=0.75); low, nonsignificant heterogeneity was observed (I^2 27%, p=0.19). The percent change in $\dot{V}O_{2peak}$ following exercise training was not different between sexes (MD=+1%, 95% CI -11% to +12%, p=0.92); high, significant heterogeneity was observed (I^2 67%, p=0.005).

Sub-analyses. Subgroup analyses for $\dot{V}O_{2peak}$ are summarized in Appendix 6.4. No sex differences in changes in $\dot{V}O_{2peak}$ were observed regardless of the frequency of exercise sessions (2 days/week compared to ≥3 days/week), intensity (moderate vs. moderate-to-vigorous vs. vigorous) or duration of the program (12 weeks or less vs. >12 weeks), the exercise paradigm (continuous vs. interval training), the type (exercise only vs. multi-component program) or setting of the intervention (combination of onsite + at home vs. onsite only), or the baseline $\dot{V}O_{2peak}$ (studies with a mean $\dot{V}O_{2peak}$ less than 20 and 25 mL O_2/kg/min for females and males, respectively, compared to those with a higher $\dot{V}O_{2peak}$). The groupings, such as the baseline $\dot{V}O_{2peak}$ thresholds, were decided based on the available data to ensure sufficient studies could be grouped and compared.

Several sub-analyses that had been pre-specified in our protocol[47] could not be conducted because not enough data in each group were available (e.g., across different AF types or medical diagnoses, across different adherence). When possible, sensitivity analyses were conducted. For instance, meta-analyses comparing estimated and directly

measured $\dot{V}O_{2peak}$ changes could not be conducted as only three of the included studies estimated $\dot{V}O_{2peak}$,[39,61,64] one of which recruited males only. Sensitivity analyses in studies using directly measured $\dot{V}O_{2peak}$ revealed similar findings (n=9 exercise interventions, 89 females, 182 males; MD=+0.32, 95% CI -1.10 to +1.75 mL O_2/kg/min, p=0.44). Additional sensitivity analyses including patients with non-permanent AF (n=6 exercise interventions, 69 females, 135 males, MD=+0.15, 95% CI -1.49 to +1.79 mL O_2/kg/min, p=0.86), interventions combining aerobic with resistance training (n=9 exercise interventions, 103 females, 201 males; MD=+0.11, 95% CI -1.30 to +1.51 mL O_2/kg/min, p=0.88), or removing two studies with high risk of bias (n=9 exercise interventions, 90 females, 178 males; MD=-0.03, 95% CI -1.51 to +1.44 mL O_2/kg/min, p=0.97) did not reveal sex differences in the change in $\dot{V}O_{2peak}$.

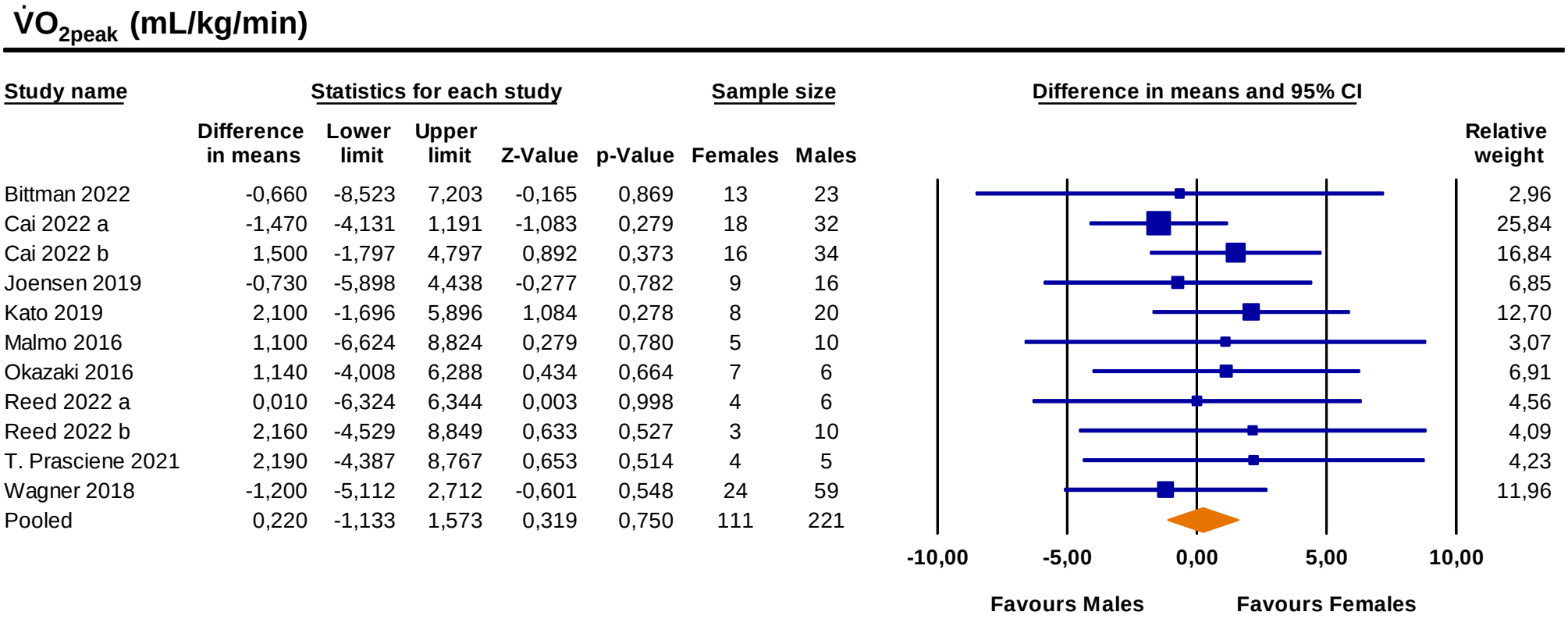


Figure 6.2. Meta-analysis comparing changes in $\dot{V}O_{2peak}$ following exercise training between females and males with atrial fibrillation.
Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Sex-specific comparisons of exercise training with control. Meta-analyses in each sex comparing the effects of exercise training with a control group on $\dot{V}O_{2peak}$ were not significant (see Figure 6.3.a-b). In females, there was a mean difference of +0.36 mL O_2/kg/min (n=5 trials, 95% CI -2.13 to +2.85 mL O_2/kg/min, p=0.78; low, nonsignificant heterogeneity: I^2 12%, p=0.50). In males, there was a mean difference of +1.02 mL O_2/kg/min (n=9 trials, 95% CI -0.79 to +2.83 mL O_2/kg/min, p=0.27; high, significant heterogeneity: I^2 75%, p<0.001).

$\dot{V}O_{2peak}$ (mL/kg/min) - Females

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	-2,130	-9,002	4,742	-0,608	0,544	17	13
Joensen 2019	3,060	-3,190	9,310	0,960	0,337	9	7
Malmo 2016	0,400	-9,749	10,549	0,077	0,938	5	3
Okazaki 2016	-0,930	-6,525	4,665	-0,326	0,745	7	5
Wagner 2018	0,700	-2,996	4,396	0,371	0,711	24	26
Pooled	0,363	-2,125	2,850	0,286	0,775	62	54

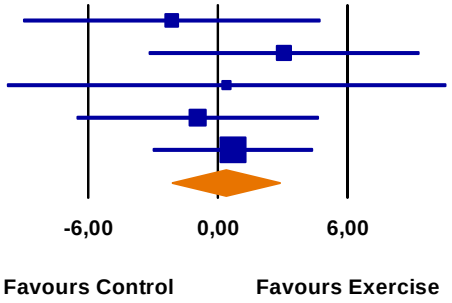


Figure 6.3.a. Meta-analysis comparing changes in $\dot{V}O_{2peak}$ following exercise training when compared to non-exercise usual care in females with atrial fibrillation.

$\dot{V}O_{2peak}$ (mL/kg/min) - Males

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Alves 2022	4,700	3,131	6,269	5,871	0,000	13	13
Bittman 2022	-1,230	-7,403	4,943	-0,391	0,696	23	21
Dabrowski 2018	-0,910	-3,303	1,483	-0,745	0,456	19	23
Joensen 2019	0,740	-4,236	5,716	0,291	0,771	16	17
Makhinova 2017	0,200	-0,357	0,757	0,703	0,482	24	24
Malmo 2016	3,600	-3,583	10,783	0,982	0,326	10	11
Melo 2019	-0,840	-6,865	5,185	-0,273	0,785	5	6
Okazaki 2016	-0,630	-5,077	3,817	-0,278	0,781	6	24
Wagner 2018	1,800	-1,149	4,749	1,196	0,232	59	64
Pooled	1,019	-0,789	2,827	1,105	0,269	175	203

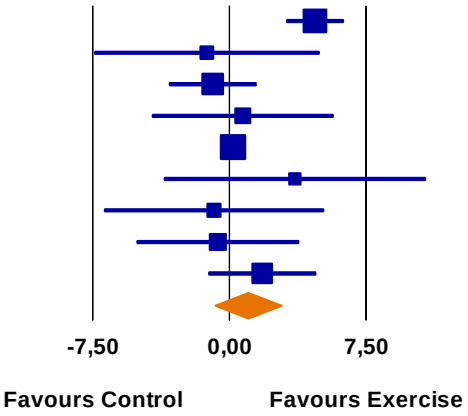


Figure 6.3.b. Meta-analysis comparing changes in $\dot{V}O_{2peak}$ following exercise training when compared to non-exercise usual care in males with atrial fibrillation.

Sex comparisons in changes in secondary outcomes following exercise training

Patient AF symptoms and AF-specific QoL. A wide range of questionnaires were used to assess AF symptoms and disease-specific QoL. Three studies used the University of Toronto Atrial Fibrillation Severity Scale (AFSS) questionnaire,[76] a measure of subjective and objective ratings of AF burden (see Figures 6.4.a-f).[41,64,70] Of these, the RACE-3 study only reported part C of the AFSS (symptom score). Four exercise interventions from two studies were, thus, included in the symptom score meta-analysis (n=62 females, n=150 males), whereas three exercise interventions were included in the other AFSS meta-analyses (n=41 females, n=78 males). Self-reported AF severity decreased less in females than males (MD=+1.00, 95% CI +0.13 to +1.87 points, p=0.02); no heterogeneity was observed (I^2 0%, p=0.70). No sex differences were observed in the other AFSS subscales (heterogeneity: frequency I^2 38%, p=0.20; duration I^2 47%, p=0.15; severity I^2 0%, p=0.45; total burden I^2 72%, p=0.03; bothered by symptoms I^2 12%, p=0.33; global well-being I^2 9%, p=0.33).

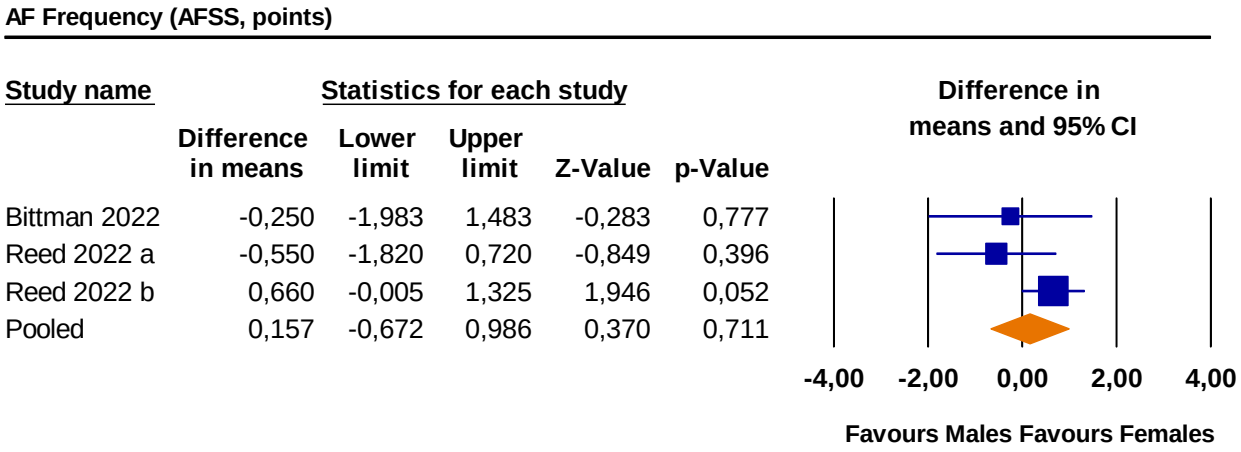


Figure 6.4.a. Meta-analysis comparing changes in patient-reported atrial fibrillation frequency following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

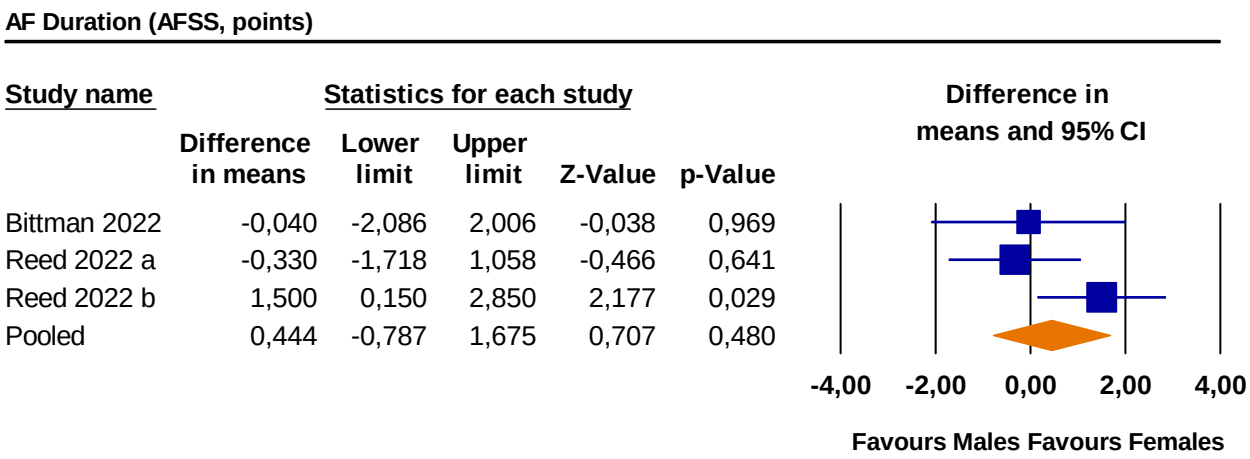


Figure 6.4.b. Meta-analysis comparing changes in patient-reported atrial fibrillation duration following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

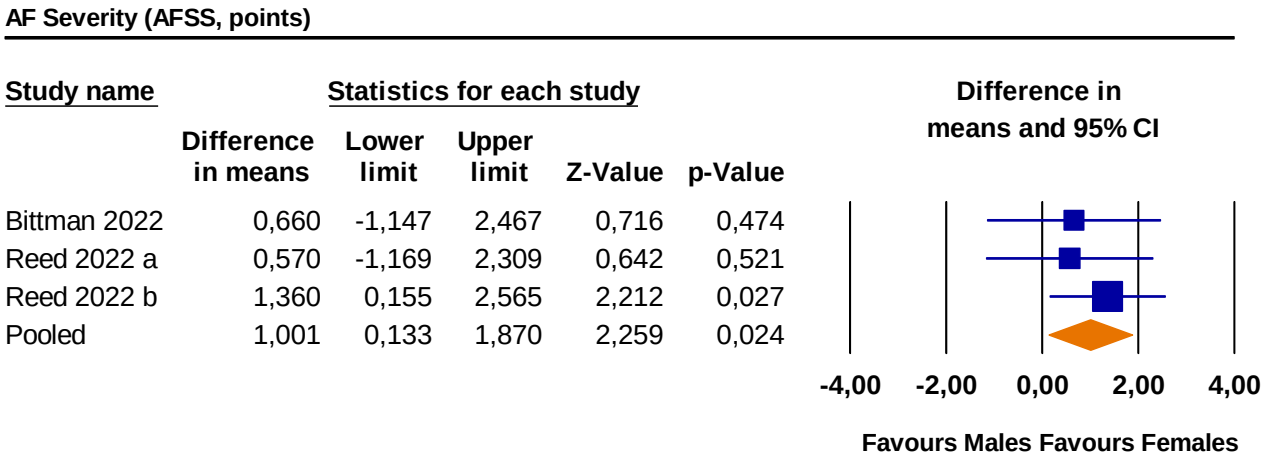


Figure 6.4.c. Meta-analysis comparing changes in patient-reported atrial fibrillation severity following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

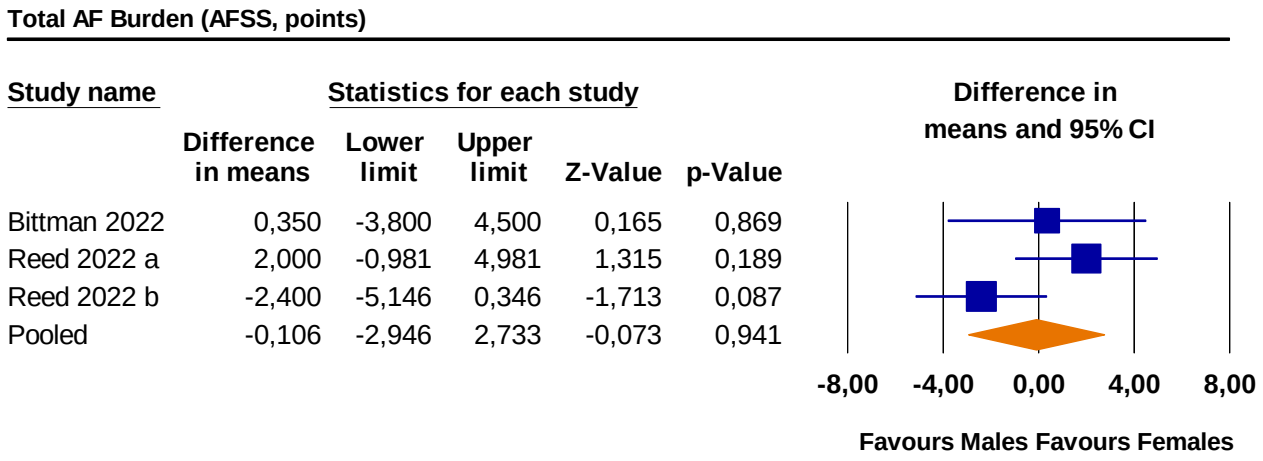


Figure 6.4.d. Meta-analysis comparing changes in self-reported total atrial fibrillation burden following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

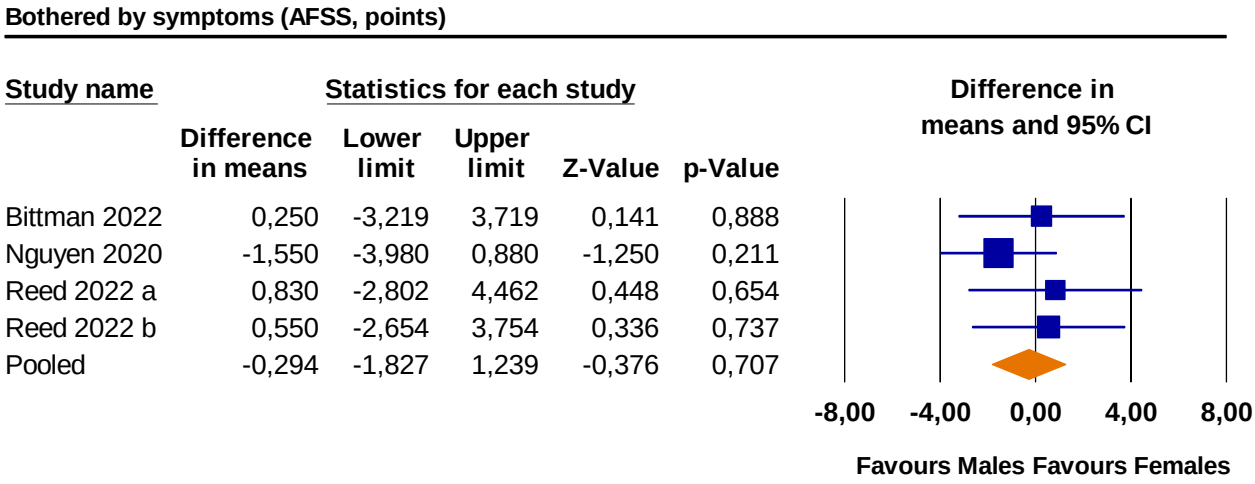


Figure 6.4.e. Meta-analysis comparing changes in the symptom score (i.e., how much patients reported being bothered by symptoms) following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

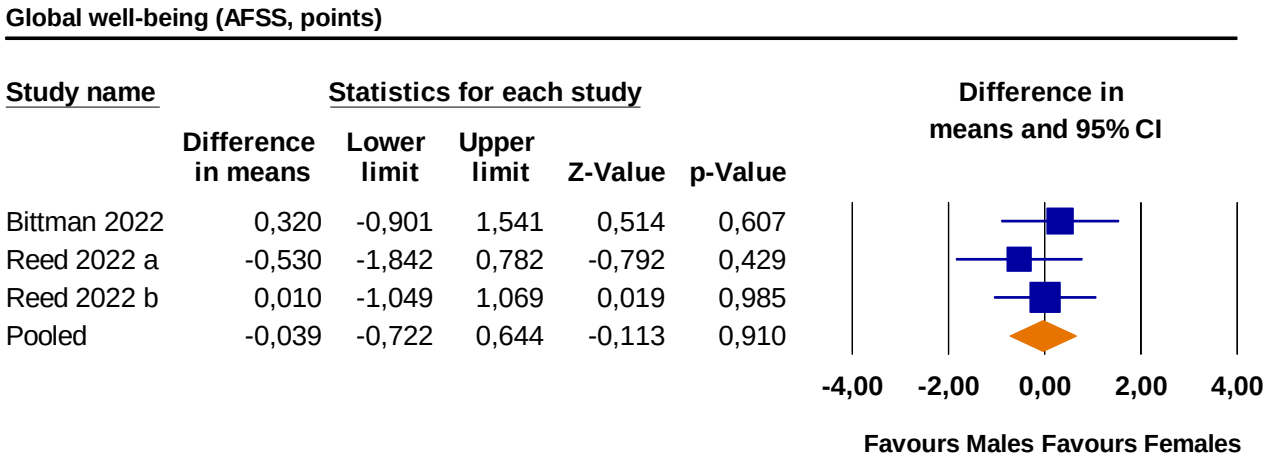


Figure 6.4.f. Meta-analysis comparing changes in self-reported global well-being following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

The remaining AF-specific QoL findings are summarized descriptively. Two studies[15,39] used the Atrial Fibrillation Effect on QualiTy of life (AFEQT, higher scores denote better QoL).[77] Joensen *et al.* only reported the global score of the AFEQT, which increased by 10 points in females and by 5 points in males following biweekly combined aerobic and strength training for 12 weeks.[39] Wagner *et al.* reported increases in the global and treatment concern scores of 34 and 17 points in females, respectively, and 20 and 12 points in males following thrice weekly combined aerobic and strength training for 12 weeks.[15] Three studies[60,67,68] in patients with AF and heart failure, one of which included males only, used the Minnesota Living with Heart Failure Questionnaire (MLHFQ, higher scores denote more severe limitations).[78] Three studies used the HeartQoL,[79,80] a questionnaire often used in patients with heart disease to measure how much their heart problems impact their QoL (higher scores denote better QoL).[67–69] The REACH-HFpEF pilot study showed improvements in the global score of the MLHFQ in both sexes (n=5 females, -11 points; n=7 males: -14 points), whilst the global HeartQoL score did not change following 12 weeks of a home-based self-managed comprehensive CR.[68] When testing the intervention in a larger sample with the REACH-HF multi-centre RCT, no improvements in either sex were observed in global MLHFQ (n=8 females, +1.1 points; n=46 males, +0.7 points) or global Heart QoL (females: +0.3 points, males: -0.1 points) at 4 months.[67] In one study, HeartQoL data were available for only one female in the exercise group, precluding sex comparisons.[69]

General patient QoL. Eight studies reported on general QoL using the SF-36.[81] This widely used questionnaire yields 8 subscale scores, and Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Higher scores denote better QoL. Subscale scores were available from seven studies; PCS and MCS scores from six studies. The meta-analyses of the change in PCS and MCS (see Figures 6.5.a-b.) were

based on ten exercise interventions and revealed no sex differences (PCS: MD=+0.66, 95% CI -1.70 to +3.01 points; MCS: MD=+1.08, 95% CI -1.46 to +3.62 points); moderate, nonsignificant heterogeneity was observed (PCS: I^2 44%, p=0.07; MCS: I^2 39%, p=0.098). The pooled analyses of ten exercise interventions (n=144 females, 319 males) revealed smaller improvements in the general health perceptions subscale of the SF-36 in females than males (MD=-3.71, 95% CI -6.88 to -0.55 points, p=0.02); low, nonsignificant heterogeneity was observed (I^2 22%, p=0.24). The mean sex difference was not significant in the remaining subscales (see Figures 6.6.a-h.); the heterogeneity was low-to-moderate (physical function: I^2 37%, p=0.12; role physical: I^2 40%, p=0.09; bodily pain: I^2 57%, p=0.01; vitality: I^2 23%, p=0.23; social function: I^2 43%, p=0.07; role emotional: I^2 32%, p=0.15; mental health I^2 23%, p=0.24). Sub-analyses were conducted to identify whether different intervention characteristics impacted our findings. No significant sex differences in changes in PCS and MCS were identified in any of the sub-analyses (see Appendix 6.5.).

Physical component summary score (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18	6,46
Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34	8,79
Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34	11,31
Cai 2022 a	1,610	-5,582	8,802	0,439	0,661	18	32	7,46
Cai 2022 b	11,780	3,671	19,889	2,847	0,004	16	34	6,27
Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22	5,88
Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81	15,96
Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27	10,07
Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28	13,32
Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59	14,46
Pooled	0,656	-1,701	3,013	0,545	0,585	155	369	

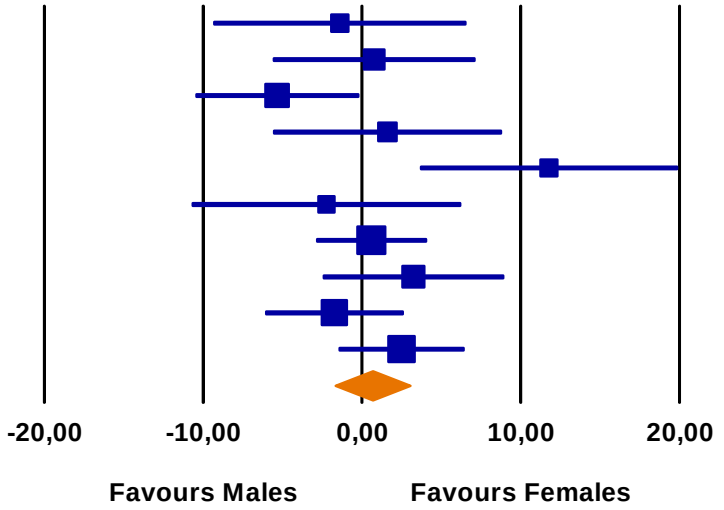


Figure 6.5.a. Meta-analysis comparing changes in the physical component summary score of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Mental component summary score (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18	4,46
Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34	9,16
Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34	13,11
Cai 2022 a	-4,470	-12,254	3,314	-1,125	0,260	18	32	7,61
Cai 2022 b	5,220	-3,315	13,755	1,199	0,231	16	34	6,65
Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20	8,74
Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81	14,57
Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27	11,51
Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28	11,01
Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59	13,18
Pooled	1,077	-1,464	3,618	0,831	0,406	153	367	

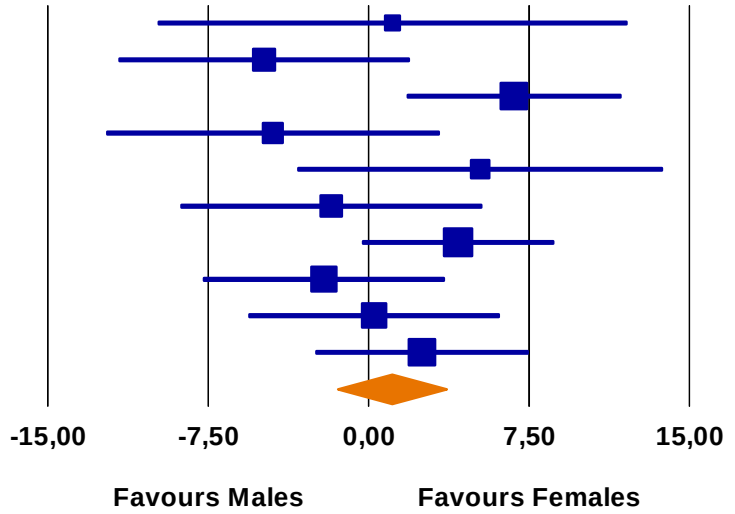


Figure 6.5.b. Meta-analysis comparing changes in the mental component summary score of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

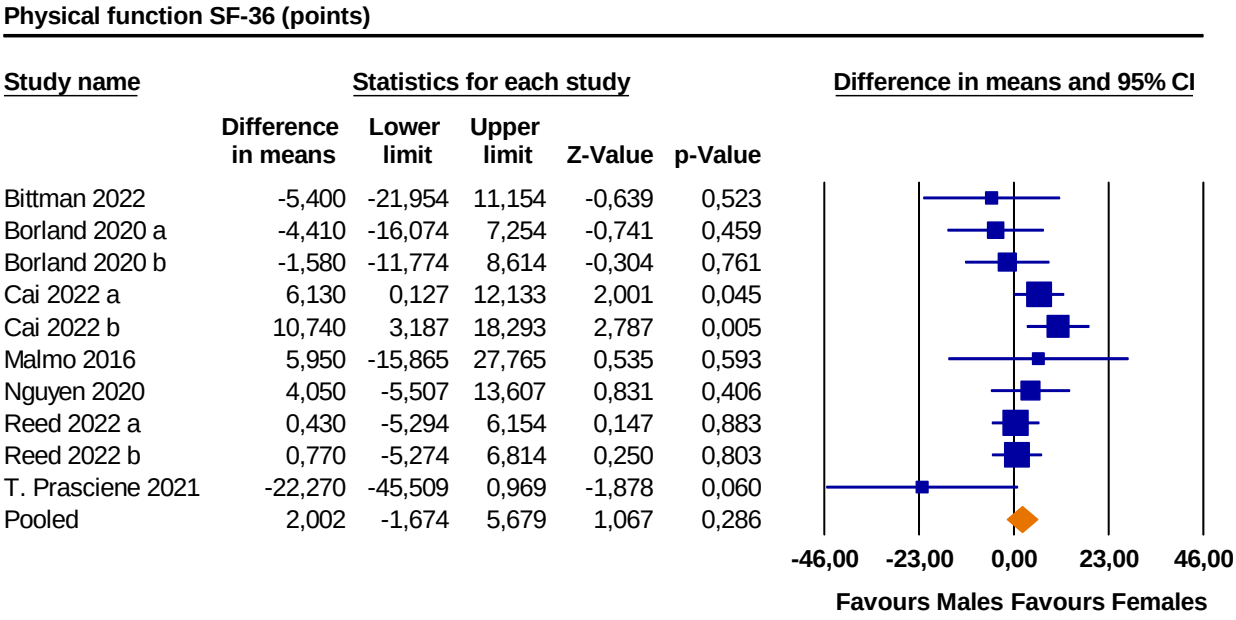


Figure 6.6.a. Meta-analysis comparing changes in the physical function subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

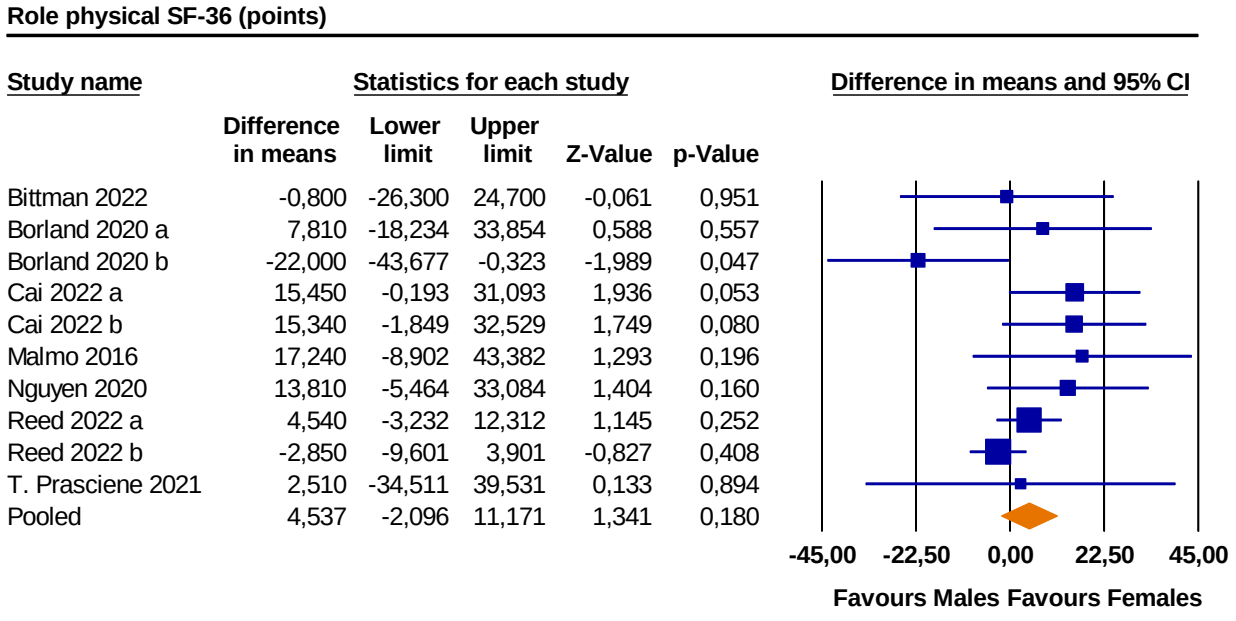


Figure 6.6.b. Meta-analysis comparing changes in the role limitations due to physical problems subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

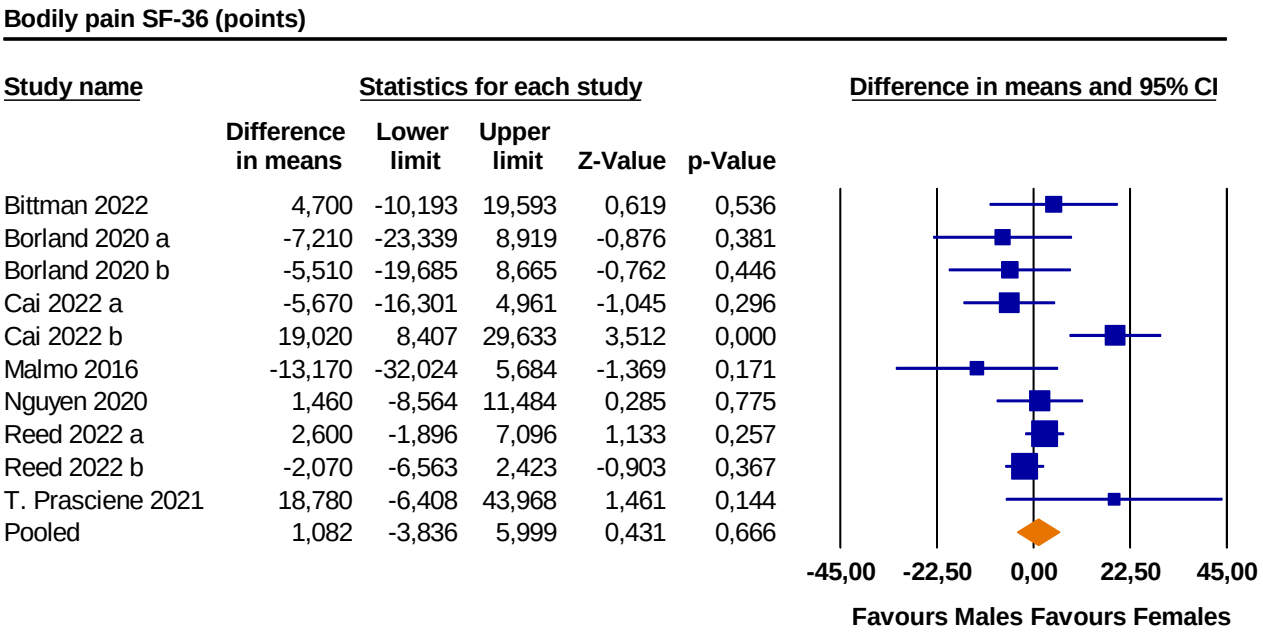


Figure 6.6.c. Meta-analysis comparing changes in the bodily pain subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

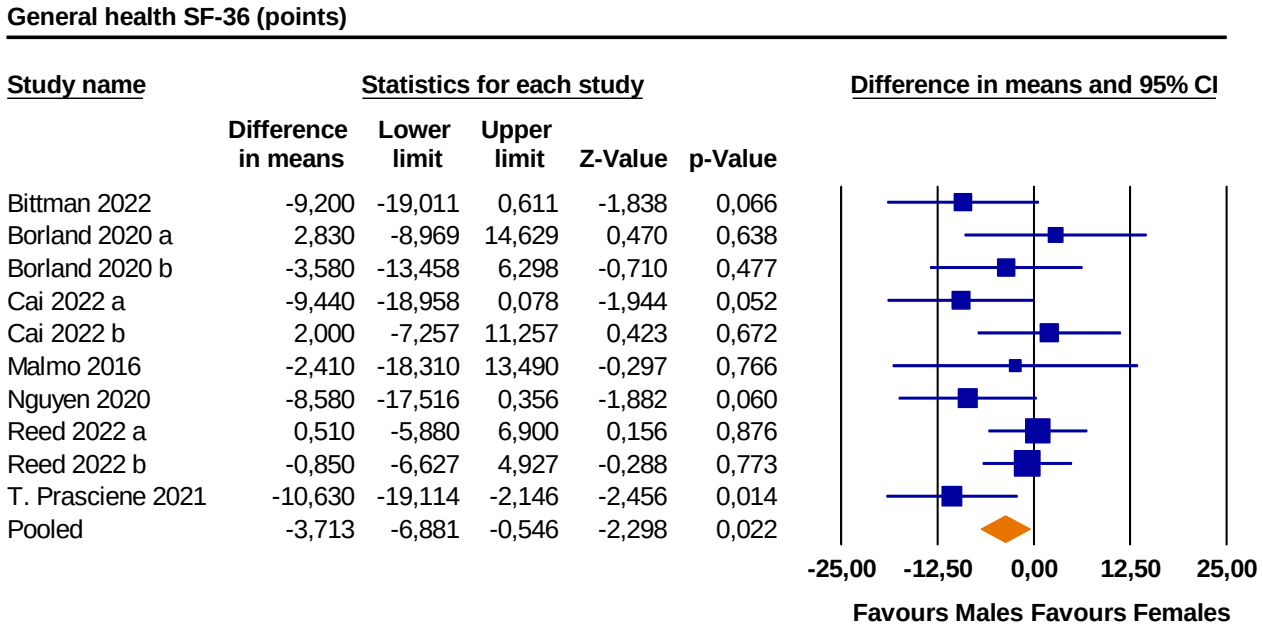


Figure 6.6.d. Meta-analysis comparing changes in the general health perceptions subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Vitality SF-36 (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	-5,400	-17,625	6,825	-0,866	0,387
Borland 2020 a	-5,940	-18,696	6,816	-0,913	0,361
Borland 2020 b	7,410	-3,935	18,755	1,280	0,201
Cai 2022 a	-2,410	-8,272	3,452	-0,806	0,420
Cai 2022 b	8,530	1,673	15,387	2,438	0,015
Malmo 2016	1,620	-14,131	17,371	0,202	0,840
Nguyen 2020	1,540	-8,090	11,170	0,313	0,754
Reed 2022 a	-1,670	-7,663	4,323	-0,546	0,585
Reed 2022 b	-2,090	-8,321	4,141	-0,657	0,511
T. Prasciene 2021	-9,890	-28,632	8,852	-1,034	0,301
Pooled	-0,040	-3,235	3,155	-0,025	0,980

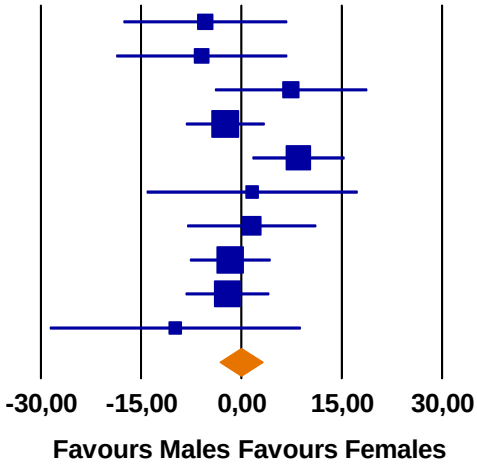


Figure 6.6.e. Meta-analysis comparing changes in the vitality subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Social function SF-36 (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	1,800	-12,141	15,741	0,253	0,800
Borland 2020 a	-9,960	-20,930	1,010	-1,780	0,075
Borland 2020 b	13,340	1,386	25,294	2,187	0,029
Cai 2022 a	-2,110	-18,706	14,486	-0,249	0,803
Cai 2022 b	8,830	-4,550	22,210	1,293	0,196
Malmo 2016	-21,870	-42,908	-0,832	-2,037	0,042
Nguyen 2020	6,510	-3,330	16,350	1,297	0,195
Reed 2022 a	3,510	-2,683	9,703	1,111	0,267
Reed 2022 b	0,430	-5,495	6,355	0,142	0,887
T. Prasciene 2021	7,840	-13,630	29,310	0,716	0,474
Pooled	1,884	-2,815	6,583	0,786	0,432

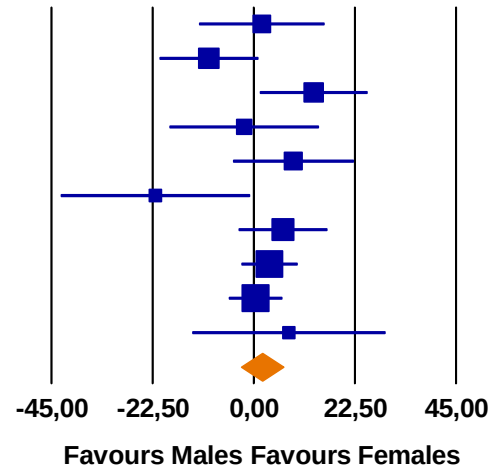


Figure 6.6.f. Meta-analysis comparing changes in the social function subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Role emotional SF-36 (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	4,800	-17,901	27,501	0,414	0,679
Borland 2020 a	-1,290	-23,003	20,423	-0,116	0,907
Borland 2020 b	10,880	-7,984	29,744	1,130	0,258
Cai 2022 a	-19,930	-37,484	-2,376	-2,225	0,026
Cai 2022 b	3,290	-15,053	21,633	0,352	0,725
Malmo 2016	-4,400	-20,025	11,225	-0,552	0,581
Nguyen 2020	1,890	-15,434	19,214	0,214	0,831
Reed 2022 a	-3,770	-10,022	2,482	-1,182	0,237
Reed 2022 b	2,130	-4,400	8,660	0,639	0,523
T. Prasciene 2021	-44,920	-83,667	-6,173	-2,272	0,023
Pooled	-1,908	-7,378	3,562	-0,684	0,494

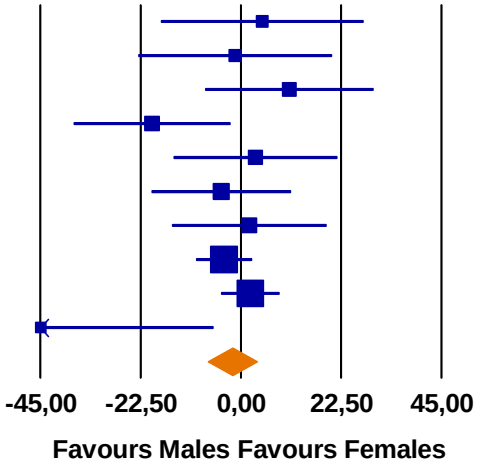


Figure 6.6.g. Meta-analysis comparing changes in the role limitations due to emotional problems subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Mental health SF-36 (points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	0,400	-9,823	10,623	0,077	0,939
Borland 2020 a	-12,000	-23,219	-0,781	-2,096	0,036
Borland 2020 b	6,400	-2,963	15,763	1,340	0,180
Cai 2022 a	6,530	0,040	13,020	1,972	0,049
Cai 2022 b	0,250	-9,442	9,942	0,051	0,960
Malmo 2016	6,800	-3,123	16,723	1,343	0,179
Nguyen 2020	0,360	-6,779	7,499	0,099	0,921
Reed 2022 a	0,080	-5,316	5,476	0,029	0,977
Reed 2022 b	-1,340	-6,193	3,513	-0,541	0,588
T. Prasciene 2021	0,170	-16,846	17,186	0,020	0,984
Pooled	1,025	-1,834	3,884	0,703	0,482

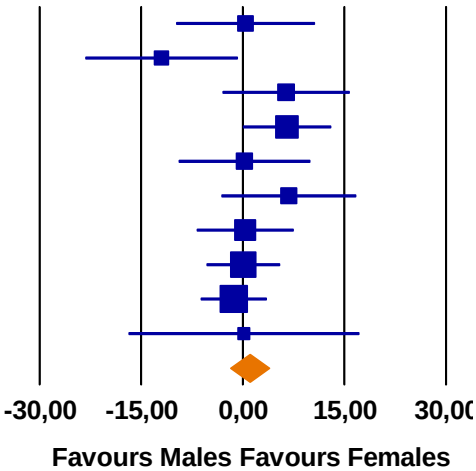


Figure 6.6.h. Meta-analysis comparing changes in the mental health subscale of the SF-36 in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Functional capacity. Nine studies reported changes in six-minute walk test distance. The mean difference between sexes was not significant (MD=-7.11, 95% CI -22.56 to 8.34 m, p=0.37, see Figure 6.7.); high, significant heterogeneity was observed (I^2 63%, p=0.005).

Hemodynamics and anthropometrics. The pooled analysis of ten exercise interventions revealed no sex differences for changes in resting HR (MD=-1.11, 95% CI -3.64 to +1.42 bpm, p=0.39, see Figure 6.8.); moderate, nonsignificant heterogeneity was observed (I^2 44%, p=0.07). Twelve interventions reported changes in resting systolic and diastolic blood pressure (see Figure 6.9.a-b.). Smaller reductions in resting systolic blood pressure were observed in females than males following exercise training (MD=+3.11, 95% CI +0.14 to +6.09 mmHg, p=0.04), moderate, nonsignificant heterogeneity was observed (I^2 42%, p=0.06). The mean difference in changes in diastolic blood pressure was not significant (MD=+1.79, 95% CI -0.18 to +3.77 mmHg, p=0.075); moderate, significant heterogeneity was observed (I^2 55%, p=0.01). The meta-analysis of changes in BMI was based on eleven exercise interventions (see Figure 6.10.). No sex differences were found in BMI changes (MD=-0.13, 95% CI -0.94 to +0.68 kg/m^2, p=0.76); low, nonsignificant heterogeneity was observed (I^2 0%, p=0.90). The pooling of three exercise interventions showed no sex differences in changes in percent body fat (MD=-1.35, 95% CI -2.15 to +4.85%, p=0.45, see Figure 6.11); moderate, nonsignificant heterogeneity was observed (I^2 50%, p=0.13).

Six-minute walk test distance (metres)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Cai 2022 a	-30,280	-59,310	-1,250	-2,044	0,041	18	31	28,32
Cai 2022 b	-6,340	-38,893	26,213	-0,382	0,703	16	32	22,52
Joensen 2019	23,750	-45,621	93,121	0,671	0,502	9	13	4,96
Kato 2019	28,000	-51,602	107,602	0,689	0,491	8	20	3,77
Mills 2020	-24,470	-72,441	23,501	-1,000	0,317	19	14	10,37
Reed 2022 a	-23,400	-103,729	56,929	-0,571	0,568	14	29	3,70
Reed 2022 b	26,020	-29,212	81,252	0,923	0,356	14	29	7,82
T.Prasciene 2021	-12,000	-74,403	50,403	-0,377	0,706	12	15	6,13
Wagner 2018	22,300	-21,575	66,175	0,996	0,319	24	59	12,40
Pooled	-7,110	-22,560	8,340	-0,902	0,367	134	242	

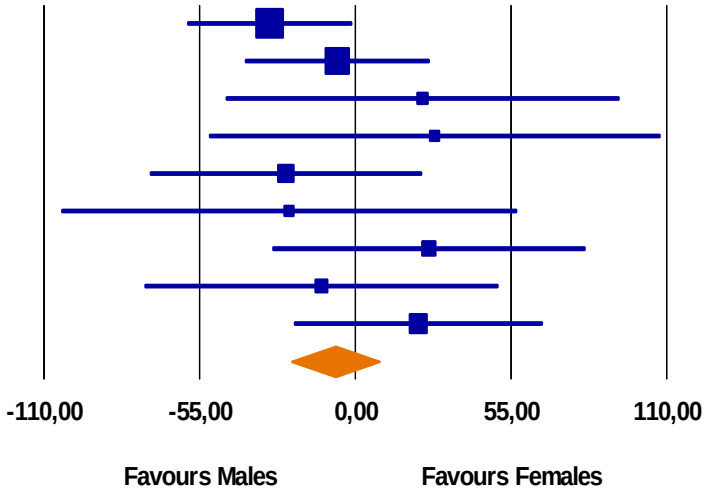


Figure 6.7. Meta-analysis comparing changes in the six-minute walk test distance in patients with atrial fibrillation following exercise training between sexes. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Resting heart rate (bpm)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Borland 2020 a	-4,000	-13,528	5,528	-0,823	0,411	12	34	7,06
Borland 2020 b	0,000	-6,587	6,587	0,000	1,000	16	34	14,78
Cai 2022 a	1,800	-4,377	7,977	0,571	0,568	18	32	16,80
Cai 2022 b	-6,160	-12,193	-0,127	-2,001	0,045	16	34	17,61
Joensen 2019	7,200	-5,425	19,825	1,118	0,264	10	16	4,02
Melo 2019	-11,500	-40,104	17,104	-0,788	0,431	2	5	0,78
Mills 2020	2,900	-6,486	12,286	0,606	0,545	19	14	7,28
Nguyen 2020	-0,850	-8,127	6,427	-0,229	0,819	25	94	12,10
Reed 2022 a	-0,360	-8,804	8,084	-0,084	0,933	14	29	8,99
Reed 2022 b	-3,040	-10,824	4,744	-0,765	0,444	14	29	10,58
Pooled	-1,111	-3,643	1,421	-0,860	0,390	146	321	

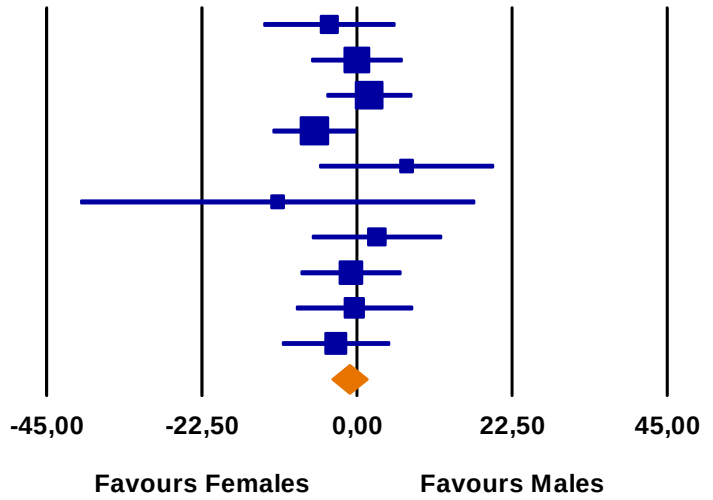


Figure 6.8. Meta-analysis comparing changes in resting heart rate in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Resting systolic blood pressure (mmHg)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Bittman 2022	2,600	-10,865	16,065	0,378	0,705	11	21	4,89
Borland 2020 a	3,000	-9,920	15,920	0,455	0,649	12	34	5,31
Borland 2020 b	0,000	-9,155	9,155	0,000	1,000	16	34	10,57
Cai 2022 a	-2,800	-10,992	5,392	-0,670	0,503	18	32	13,20
Cai 2022 b	4,710	-2,657	12,077	1,253	0,210	16	34	16,32
Joensen 2019	12,610	-8,773	33,993	1,156	0,248	9	16	1,94
Malmo 2016	14,680	4,015	25,345	2,698	0,007	6	20	7,79
Melo 2019	-2,000	-23,792	19,792	-0,180	0,857	2	5	1,87
Mills 2020	5,340	-8,015	18,695	0,784	0,433	19	14	4,97
Nguyen 2020	3,250	-3,566	10,066	0,934	0,350	25	94	19,07
Reed 2022 a	-1,020	-12,417	10,377	-0,175	0,861	14	29	6,82
Reed 2022 b	3,590	-7,462	14,642	0,637	0,524	14	29	7,25
Pooled	3,112	0,135	6,089	2,049	0,040	162	362	

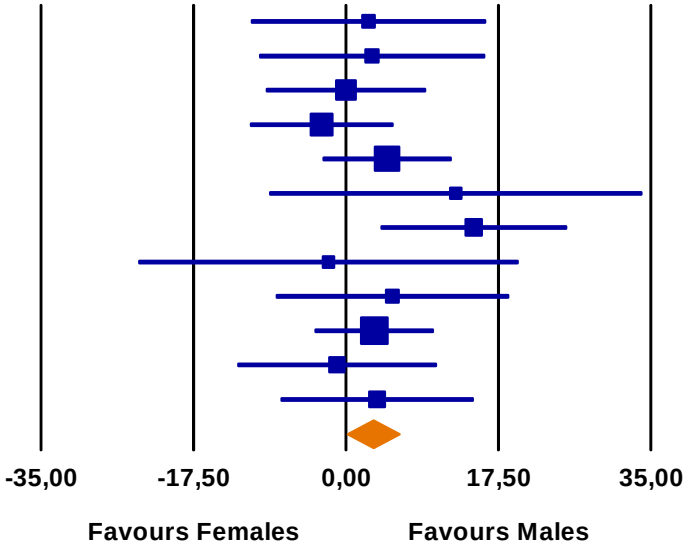


Figure 6.9.a. Meta-analysis comparing changes in resting systolic blood pressure in patients with atrial fibrillation following exercise training between sexes. Borland a: Cardiovascular rehabilitation. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Resting diastolic blood pressure (mmHg)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males	Relative weight
Bittman 2022	2,600	-4,643	9,843	0,704	0,482	11	23	7,44
Borland 2020 a	-1,000	-7,813	5,813	-0,288	0,774	12	34	8,40
Borland 2020 b	2,000	-4,397	8,397	0,613	0,540	16	34	9,53
Cai 2022 a	1,730	-3,838	7,298	0,609	0,543	18	32	12,58
Cai 2022 b	-3,190	-9,636	3,256	-0,970	0,332	16	34	9,39
Joensen 2019	14,360	0,001	28,719	1,960	0,050	9	16	1,89
Malmo 2016	3,750	-4,767	12,267	0,863	0,388	6	20	5,38
Melo 2019	4,500	-10,188	19,188	0,600	0,548	2	5	1,81
Mills 2020	9,000	1,429	16,571	2,330	0,020	19	14	6,81
Nguyen 2020	0,880	-3,560	5,320	0,388	0,698	25	94	19,79
Reed 2022 a	1,210	-5,143	7,563	0,373	0,709	14	29	9,67
Reed 2022 b	1,580	-5,725	8,885	0,424	0,672	14	29	7,31
Pooled	1,792	-0,183	3,767	1,778	0,075	162	364	

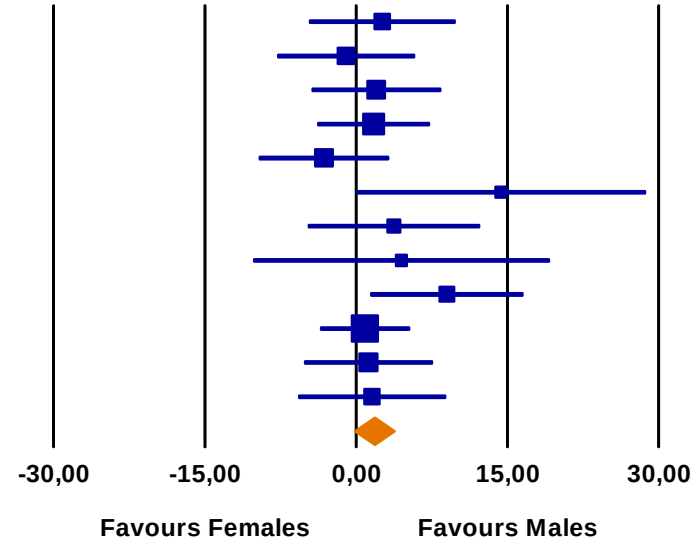


Figure 6.9.b. Meta-analysis comparing changes in resting diastolic blood pressure in patients with atrial fibrillation following exercise training between sexes. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

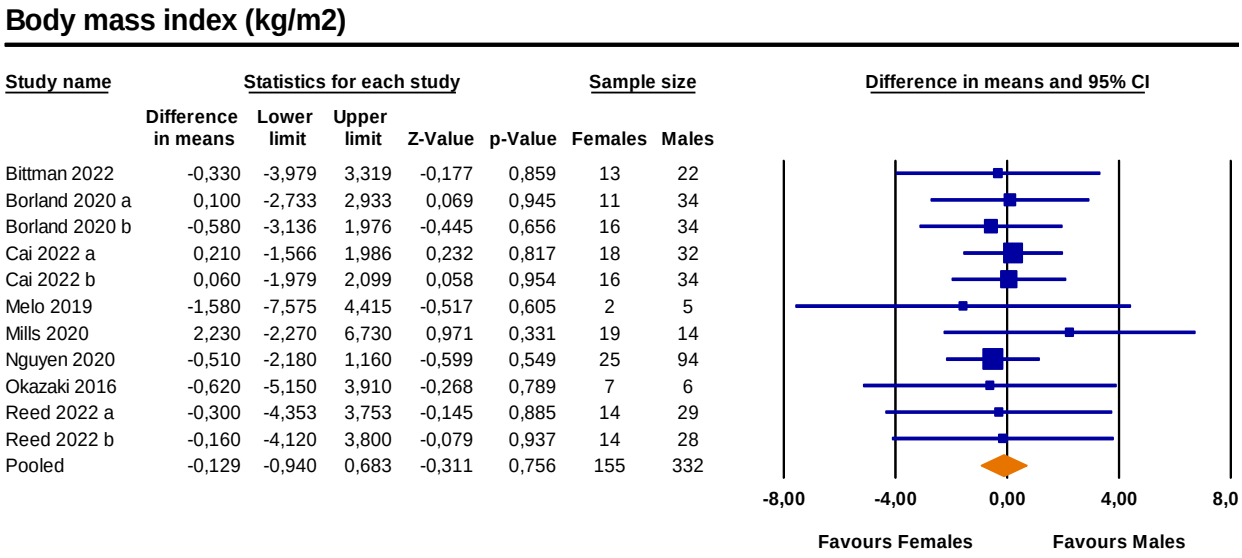


Figure 6.10. Meta-analysis comparing changes in body mass index in patients with atrial fibrillation following exercise training between sexes. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

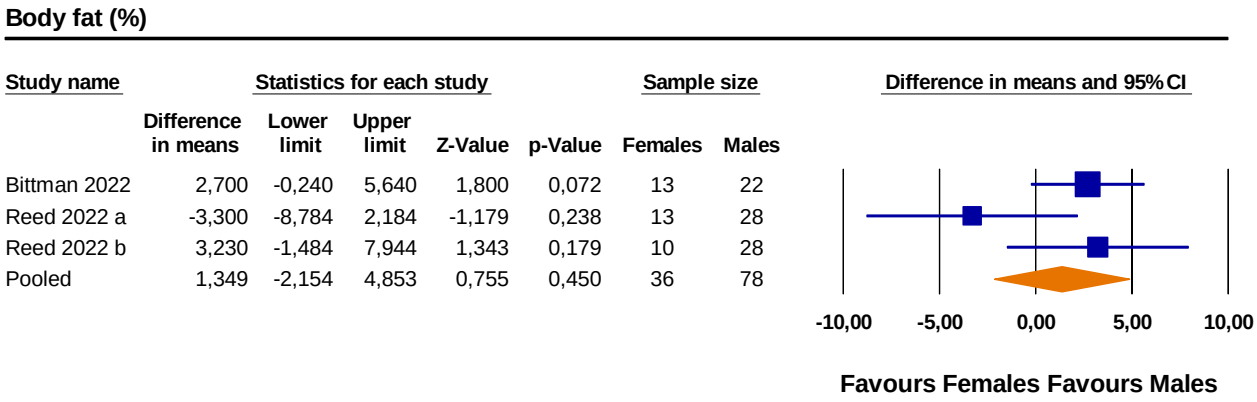
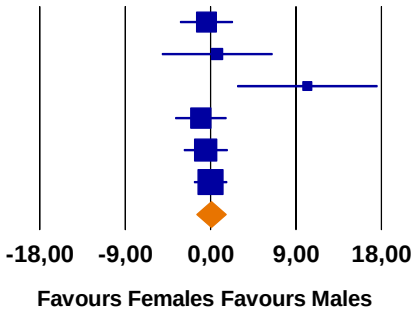


Figure 6.11. Meta-analysis comparing changes in percent body fat in patients with atrial fibrillation following exercise training between sexes. Borland b: Physical activity prescription. Cai a: Conventional cardiovascular rehabilitation combined with telemedicine. Cai b: Conventional cardiovascular rehabilitation. Reed a: MICT. Reed b: HIIT. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Anxiety and depression. Several self-report tools were used to assess anxiety and depression, including the Hospital Anxiety and Depression Scale (HADS, n=6 studies, of which one included males only),[15,41,61,67–69] the Patient Health Questionnaire (PHQ-8, n=1[64] and PHQ-9, n=2)[32,39] and the General Anxiety Disorder (GAD-7, n=3 studies) scale.[32,39,64] Evidence from pooled analysis of six exercise interventions (n=60 females, n=161 males, see Figure 6.12.) revealed no sex differences in changes in anxiety (MD=+0.06, 95% CI -1.49 to +1.60 points; moderate, nonsignificant heterogeneity, I^2 39%, p=0.15) or depression (MD=+0.01, 95% CI -1.64 to +1.63 points; moderate, significant heterogeneity, I^2 60%, p=0.03). The pooling of three studies (n=42 females, 53 males, see Figure 6.13.) did not reveal sex differences in changes in anxiety as measured by the GAD-7 (MD=-1.00, 95% CI -2.94 to +0.93 points, p=0.31; low, nonsignificant heterogeneity, I^2 0%, p=0.84). One study in patients with AF and cardiovascular implantable electronic devices used the Beck Depression Inventory questionnaire;[82] the only female in the CR group experienced a 1-point reduction in depression,[73] and in males (n=21) depression decreased by 4 points.

Anxiety (HADS, points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Dalal 2019	-0,430	-3,203	2,343	-0,304	0,761
Lang 2018	0,690	-5,122	6,502	0,233	0,816
Melo 2019	10,200	2,820	17,580	2,709	0,007
Reed 2022a	-1,020	-3,714	1,674	-0,742	0,458
Reed 2022b	-0,510	-2,797	1,777	-0,437	0,662
Wagner 2018	0,000	-1,736	1,736	0,000	1,000
Pooled	0,057	-1,486	1,601	0,073	0,942



Depression (HADS, points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Dalal 2019	-1,070	-3,197	1,057	-0,986	0,324
Lang 2018	-0,890	-4,742	2,962	-0,453	0,651
Melo 2019	10,220	4,147	16,293	3,299	0,001
Reed 2022a	-0,020	-2,108	2,068	-0,019	0,985
Reed 2022b	-0,790	-3,469	1,889	-0,578	0,563
Wagner 2018	-0,600	-2,035	0,835	-0,820	0,412
Pooled	-0,005	-1,642	1,632	-0,006	0,995

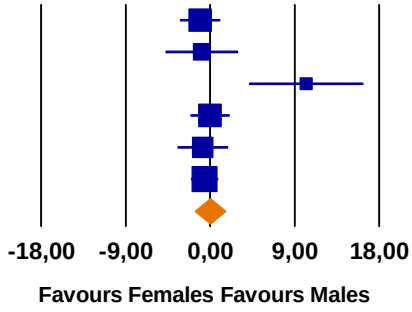


Figure 6.12. Meta-analysis comparing changes in anxiety and depression as measured by the Hospital Anxiety and Depression Scale (HADS) in patients with atrial fibrillation following exercise training between sexes. Reed a: Moderate- to vigorous-intensity continuous training. Reed b: High-intensity interval training.

Anxiety (GAD-7, points)

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	-1,250	-4,016	1,516	-0,886	0,376
Joensen 2019	-0,210	-4,309	3,889	-0,100	0,920
Mills 2020	-1,200	-4,786	2,386	-0,656	0,512
Pooled	-1,004	-2,936	0,927	-1,019	0,308

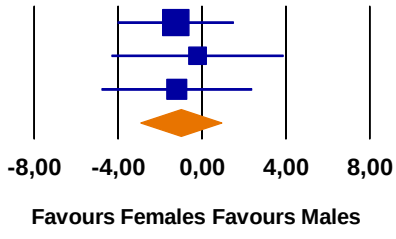


Figure 6.13. Meta-analysis comparing changes in anxiety as measured by the General Anxiety Disorder (GAD)-7 in patients with atrial fibrillation following exercise training between sexes.

Physical activity. The method for physical activity monitoring and reporting differed significantly between studies. One study calculated the proportion of patients who reported meeting or not at least 150 minutes per week of moderate-intensity or at least 75 minutes per week of vigorous-intensity physical activity.[70] Another study reported the proportion of patients in the low, moderate or high categories based on the self report International Physical Activity Questionnaire (IPAQ).[65] Two studies reported minutes per week of MVPA as measured by a triaxial accelerometer.[35,41] Thus, changes in physical activity levels could not be compared between sexes in the form of a meta-analysis. The RACE study reported an increase in the proportion of patients meeting the physical activity guidelines by 32% in females and 10% in males.[70] Twelve weeks of telerehabilitation combined with conventional CR led to an increase in the proportion of patients in the "high" physical activity category, based on the IPAQ, by +28% in females and +57% in males; whereas conventional CR alone led to a +6% and +16% increase in females and males, respectively.[65] Following 12 weeks of either supervised CR or a physical activity prescription, the physical activity levels decreased in males (-41 minutes per week of MVPA and -7 minutes per week of MVPA, respectively), and females' physical activity levels decreased following CR (-34 min per week of MVPA) and increased following a physical activity prescription (+57 min per week of MVPA).[35] Further, twelve weeks of MICT led to a 14- and 46-minute increase in weekly MVPA in females and males, and twelve weeks of HIIT to a 35- and 55-minute increase in weekly MVPA in females and males, respectively.[41]

Sex-specific changes in secondary outcomes following exercise training when compared to usual care

Sixteen meta-analyses were conducted comparing the effects of exercise with control in females (see Appendix 6.6). The sample size of these female-only meta-analyses was small. The largest sample size was available for $\dot{V}O_{2peak}$, MCS and PCS (exercise group: n=62; control group: n=54), and the smallest for the SF-36 subscales, anxiety and depression (exercise group: n=38; control group: n=38). Thus, these results should be interpreted with caution. No significant effects were seen in any of the female-only meta-analyses. A trend for greater improvements in the PCS (n=4 studies, MD=+3.29, 95% CI -0.22 to +6.79 points, p=0.06; low, nonsignificant heterogeneity I^2 0%, p=0.73) and the social functioning subscale (n=3 studies, MD=+7.31, 95% CI -2.87 to +17.49 points, p=0.160; moderate, nonsignificant heterogeneity I^2 50%, p=0.09) scores following exercise training when compared to control was observed in females.

Eighteen meta-analyses were conducted comparing the effects of exercise training with control in males (see Appendix 6.7.). The largest sample size was available for $\dot{V}O_{2peak}$ (exercise group: n=175; control group: n=203) and blood pressure (exercise group: n=201; control group: n=224); and the smallest for the SF-36 subscales (exercise group: n=119; control group: n=120). Among the male-only meta-analyses comparing the effects of exercise training with a control group, significantly greater improvements in the exercise group were observed in the PCS score (n=4 studies, MD=+1.60, 95% CI +0.05 to +3.16 points, p=0.044; low, nonsignificant heterogeneity I^2 20%, p=0.29), general health (n=3 studies, MD=+9.50, 95% CI +4.82 to +14.17 points, p<0.001; low, nonsignificant heterogeneity I^2 0%, p=0.52) and vitality (n=3 studies, MD=+9.84, 95% CI +1.15 to +18.53 points, p=0.026; moderate, nonsignificant heterogeneity I^2 58%, p=0.091) subscales, resting HR (n=6 studies, MD=-6.62, 95% CI -12.89 to -0.35 bpm,

p=0.039; high, significant heterogeneity I^2 72%, p=0.002) and diastolic blood pressure (n=8 studies, MD=-2.89, 95% CI -5.31 to -0.78 mmHg, p=0.019; high, significant heterogeneity I^2 74%, p<0.001), and anxiety severity (n=4 studies, MD=-1.17, 95% CI -2.08 to -0.27 points, p=0.011; low, nonsignificant heterogeneity I^2 0%, p=0.46).

Adherence with the exercise programs and adverse events

Seven investigators provided us with sex-specific data regarding participants' adherence to the exercise program by sex.[32,35,41,65,70,72,73] These data are summarized descriptively. Eight exercise interventions reported the number of exercise sessions prescribed (range: 17 to 48 sessions) and attended during the program. Females attended between 12[32] and 42[35] exercise sessions, with a pooled mean of 22.5±3.5 number of sessions; males attended between 16[32] and 42[35] sessions, with a pooled mean of 22.2±3.6 number of sessions. Nine exercise interventions reported the proportion of sessions attended.[32,35,41,65,70,73] The pooled mean exercise adherence was 5% lower in females than males (F: 81% vs. M: 86% exercise sessions attended). All studies reported high (≥70% sessions attended) adherence, except for a 12-week conventional, supervised CR program reporting a 39% adherence in females and 56% in males.[65] Compliance with the exercise prescription (i.e., whether patients were exercising at the prescribed intensity) was rarely reported.[41] Dropout data were not available by sex and, thus, are not reported. In the RACE study (25 females in intervention and 27 in control; 94 males in intervention and 99 in control), 4 and 5 severe adverse events were reported in females in the control and intervention groups, respectively, and 15 and 17 severe adverse events were reported in males in the control and intervention groups, respectively.[70] Bittman *et al*., reported three adverse events during the study unrelated to

the intervention (i.e., acute heart failure, hip fracture and an ablation).[64] Two studies did not report any adverse events[61,65] and most authors did not provide their data by sex.

6.6. Discussion

Study 4 systematically reviewed and analyzed available data comparing the change in physical and mental health outcomes following exercise training between females and males with AF. Contrary to our hypothesis, the pooled analysis of published and unpublished data did not reveal differences in $\dot{V}O_{2peak}$ changes between sexes following exercise training programs implementing 23- to 65-min exercise sessions of combined aerobic and resistance training, two to six days per week for 12 weeks to one year (n=8 studies, MD=+0.22, 95% CI -1.13 to +1.57 mL O_2/kg/min). $\dot{V}O_{2peak}$ increased by 15% in females and by 14% in males. Patient-reported severity of AF decreased significantly less in females than males (MD=+1.00, 95% CI +0.13 to +1.87 points) and general health perceptions increased significantly less in females (MD=-3.71, 95% CI -6.88 to -0.55 points) following exercise training. In line, reductions in systolic blood pressure with exercise training were significantly smaller in females than males (MD=+3.11, 95% CI +0.14 to +6.09 mmHg). Less than one third of participants were females, even though females represent 47% of patients with AF globally.[1]

Primary outcome: $\dot{V}O_{2peak}$

A small nonsignificant difference of 0.22 mL O_2/kg/min was reported following exercise training. No meta-analyses to date have compared the effects of exercise training between females and males with AF; making it difficult to contextualize our results. Two studies in patients with AF have reported $\dot{V}O_{2peak}$ data by sex, yet did not conduct sex-based analyses.[5,15] For instance, a 12-month walking intervention in patients with permanent AF (n=7 females, 13 males) led to an increase in $\dot{V}O_{2peak}$ of 7%

in females and 18% in males.[5] Contrary to our finding, a previous meta-analysis demonstrated a significantly smaller $\dot{V}O_{2peak}$ improvement following HIIT in females than males with coronary artery disease (MD=-1.10, 95% CI -2.08 to -0.12 mL O_2/kg/min, p=0.03).[43] A few studies in patients with CVD have failed to identify sex differences in $\dot{V}O_{2peak}$ changes between sexes.[42,83] The striking female under-representation may have previously limited the quality of sex-based analyses.[13,14,42,83]

The pooled mean $\dot{V}O_{2peak}$ at baseline from our available data was 18.7 mL O_2/kg/min in females and 22.6 mL O_2/kg/min in males with AF. These values are higher than the average reported in patients with CVD at CR entry (females: 15 mL O_2/kg/min, males: 19 mL O_2/kg/min)[84] and in patients with AF (~15 mL O_2/kg/min).[5] In turn, this may limit the generalizability of findings to a minority of patients who are fitter and have less co-morbidities, and may leave less room for improvement. At follow-up, a 3.1 mL O_2/kg/min difference between sexes remained. This near 1 MET (i.e., 3.5 mL O_2/kg/min) sex difference may be clinically significant: in patients with AF, every 1 MET higher $\dot{V}O_{2peak}$ has been associated with a lower risk for all-cause (hazard ratio: 0.88, 95% CI 0.81 to 0.95) and CVD mortality (hazard ratio: 0.85, 95% CI 0.76 to 0.95), and morbidity (hazard ratio: 0.88, 95% CI 0.82 to 0.95).[11] None of the sub-group or sensitivity analyses revealed different findings. Thus, our results and those from other meta-analyses[12,31,85–88] have not led to a consensus on the optimal exercise prescription targets for females and males with AF. This contrasts with the specific exercise targets (i.e., aerobic exercise: ≥200 min per week of moderate intensity; resistance: 2 to 3 days per week; flexibility: ≥10 min per day at least 2 days per week in those ≥65 years of age) endorsed by the CCS/CHRS AF management guidelines.[4]

$\dot{V}O_{2peak}$ changes with exercise training compared to rest in each sex

These results should be interpreted with caution given the limited data available for the sex-specific meta-analyses of the effects of exercise training when compared to usual care. This was, in part, due to our inability to obtain sex-specific data from 42 eligible studies, and due to several studies comparing two exercise interventions and, thus, being excluded from the exercise vs. control examination. The nonsignificant $\dot{V}O_{2peak}$ changes in females and males when compared to a non-exercise usual care may have resulted from the above than average $\dot{V}O_{2peak}$ at baseline, high heterogeneity in males (I^2 75%) and limited data available in females (n=62 in the exercise group and 54 in the control group). Although most male-centric meta-analyses in patients with AF have reported significant changes in $\dot{V}O_{2peak}$,[12,85,86] others have not.[88] Future exercise trials may benefit from implementing greater exercise volumes or intensities to enhance $\dot{V}O_{2peak}$ improvements. Although we did not identify differences between interval when compared to continuous exercise training, designing protocols that allow for the maintenance of a high percentage of $\dot{V}O_{2peak}$ for a long duration (i.e., HIIT) has been recommended to maximize improvements in $\dot{V}O_{2peak}$.[89] The feasibility of such approaches deserves further examination in populations who are typically older, frail, deconditioned and anxious about exercise training, such as those with AF.[90–92]

Secondary outcomes

None of the included studies originally performed sex-based analyses of the secondary outcomes. The AFSS meta-analyses should be interpreted with caution as only three exercise interventions from two studies were included. Following exercise training, females did not benefit as much as males in several secondary outcomes, including improvements in self-reported severity of AF, general health perceptions and reductions in systolic and diastolic blood pressure. The reasons for such disparities are unclear. Baseline values were similar between sexes, except for the general health score, which

was lower in females (52.8 points vs. 56.2 points) and increased by 4 points less following exercise training when compared to males. The needs of females may not be met with current exercise training offerings.[93] Previous sub-group analyses in patients with AF identified that aerobic conditioning, yoga and exercise sessions of at least 60 minutes in duration led to greater improvements in QoL and functional capacity.[85] Females may require a more aggressive exercise intervention (e.g., longer exercise sessions), or a more integrated, holistic care approach to improve their general QoL. In support, although our sub-analyses in PCS and MCS scores did not reveal sex differences, the MD in the PCS change score was 1.2 points in favour of males in studies that implemented exercise only, when compared to 2.4 points in favour of females in studies that implemented multi-component interventions. Interestingly, the largest sample size was available for changes in blood pressure (n=162, 31% females, n=362 males). This may have facilitated detecting sex differences, underscoring the importance of enhancing the recruitment of females in future trials. Contrary to our findings, our previous meta-analysis in patients with coronary artery disease revealed no sex differences in blood pressure reductions (n=6 studies, systolic: MD=-2.51, 95% CI -6.57 to 1.55 mmHg, p=0.23; diastolic: MD=-0.91, 95% CI -4.98 to 3.15 mmHg, p=0.66) and lower improvements in BMI (n=10 studies, MD=-0.25, 95% CI -0.03 to -0.47 kg/m^2, p=0.02) in females than males following HIIT.[43]

Not enough data were available to perform meta-analysis in AF-specific QoL as a wide range of tools were used across different studies. The CopenHeartRFA trial led to significant increases in AF-specific QoL as measured by the AFEQT in females (global score: +34±17 points; treatment concern score: +17±24 points) but not males, when compared to usual care.[15] Similarly, Joensen *et al.* reported a 5-point greater increase in the global AFEQT score in females than males. It remains unclear whether

exercise training may narrow pre-existing differences in QoL between sexes. Further, elevated symptoms of anxiety and depression are present in more than one third of patients with AF[94] and they negatively impact their QoL.[95,96] Changes in anxiety and depression did not differ between sexes following 12-week exercise programs delivered at home or in the hospital.[41,67–69] The pooled baseline means of anxiety and depression as measured by the HADS were in the normal range (≤7 points), with scores of 5.7 and 4.2 in females, respectively, and 4.9 and 4.0 points in males. This leaves little room for improvement. Ceiling effects may have reduced our ability to detect sex differences.

Meta-analyses in the change in physical activity levels could not be conducted as only four studies reported this outcome, two of which used self report scales[65,70] and two triaxial accelerometers.[35,41] Although this has not been statistically examined, the RACE study reported greater improvements in the physical activity levels in females than males following moderate-intensity aerobic conditioning (+32% vs. +10% meeting the guidelines).[70] A walking physical activity prescription led to increases in MVPA levels in females only (+57 minutes per week),[35] whilst 12 weeks of HIIT did not increase MVPA levels in either sex.[35] Following telerehabilitation combined with conventional CR, the proportion of patients in the "high" physical activity category of the IPAQ increased by 29% less in females than males.[65] Further, MICT and HIIT led to a +21 and +9 smaller increase in weekly minutes of MVPA in females than males.[41] Regular physical activity brings lifelong benefits. In the HUNT-3 study (n=1,117 patients, 31% females), patients with AF meeting the physical activity guidelines for healthy adults had a 45% lower risk of all-cause and CVD mortality, when compared to those who self-reported being inactive.[11] Thus, increasing the physical activity levels of patients with AF is an important outcome from behaviour change interventions.[97] Current sex-specific evidence regarding changes in physical activity levels following

exercise training is inconclusive, as it remains unclear whether both sexes are able to increase their MVPA levels after engaging in exercise training.

Changes in secondary outcomes with exercise training compared to rest in each sex

No sex-specific meta-analyses in changes in patient AF symptoms, AF-specific QoL or physical activity levels were conducted in either sex comparing exercise training with usual care. Further, changes in bodily pain and resting HR were not examined in females given the limited data available. The sex-specific meta-analyses presented should be interpreted with caution as the sample sizes ranged between 38 to 65 per group in females, and 119 and 224 per group in males. We could surmise that the small number of female participants may have precluded finding significant effects of exercise training when compared to usual care. For instance, a mean difference of more than 3 points in the PCS and MCS score was found favouring exercise training in females, yet it did not reach statistical or clinical significance. In contrast, several significant effects were seen in males following exercise training when compared to usual care, including improvements in the PCS, general health and vitality scores, resting HR, diastolic blood pressure and anxiety symptoms. Such results align with previous meta-analyses, as exercise training has been shown to improve QoL[12,85,87,88,98] and resting HR[85] in patients with AF. Fewer, inconclusive data are available for blood pressure and anxiety.[88]

It is noteworthy that even though no sex differences were found in the change of most of our outcomes, some follow-up measures remained poorer in females than males with AF. For instance, the pooled follow-up means for PCS (F: 46 vs. M: 51 points), MCS (F: 53 vs. M: 58 points) and 6MWT (F: 480 vs. M: 561 points) remained lower in females. These differences are clinically significant (5-point difference[99] and 54-metre difference,[100] respectively). Thus, the question arises as to whether we can be satisfied

with these findings or, whether working towards more equitable research and care means we should strive for females and males to reach similar levels of health status following an exercise intervention.[101] Our results suggest that the latter may require additional approaches for females with AF.

Additional considerations for the interpretation of findings

The risk of bias was high in 5 studies and the certainty of evidence was low-to-very low across all outcomes assessed. Higher-quality studies are warranted before we can establish clear conclusions in sex-specific exercise research in patients with AF. We are cognizant that none of the included trials were designed to compare the effects of the intervention between sexes. Together with the 3-fold lower female participation, this may limit our ability to detect sex differences. This further emphasizes the need to continue working towards implementing more inclusive methodologies in clinical research.[101] Engaging local citizens and patient advocacy groups, removing unjustified sex-specific exclusion criteria and building diverse research teams are some suggestions to achieve representative enrollment in trials including patients with AF.[101]

Strength and limitations

Our systematic review has several strengths. We pooled published and unpublished data from contemporary (from 2016) trials across four continents to conduct sex-based analyses. We included critical objective (e.g., $\dot{V}O_{2peak}$) and self-reported (e.g., QoL) measures encompassing physical and mental health to address research gaps regarding sex-based differences in the response to exercise training in the AF population. We followed systematic review methodological standards including the PRISMA and SAGER guidelines, TESTEX risk of bias evaluation and the GRADE approach. Further, to enhance the generalizability of findings, we deemed eligible a wide range of patients with AF, including any AF type and those with additional co-morbidities such

as heart failure. Several limitations should be considered. The majority (12/16) of trials were conducted in Europe, and most participants were of European ancestry. Of the 60 eligible studies, only one study reported outcomes by sex and only data from 18 studies were available. Many authors declined or did not reply to our request of data sharing by sex. This led to several outcomes not being included in our analyses, and some meta-analyses having small sample sizes. Such difficulties have been previously reported[43] and they stagnate the advancement of research towards more inclusive, sex-specific evidence. The authors propose the use of data repositories to ensure the long-term preservation of data and facilitate data sharing across organizations. Finally, the certainty of the evidence from the GRADE assessment was low-to-very low. The quality was downgraded across all outcomes due to indirectness from the predominantly male representation; less than one third of participants were females.

6.7. Conclusion

This systematic review and meta-analyses addressed the lack of sex-based analyses in previous exercise studies in patients with AF; a necessary first step to provide evidence-based exercise recommendations for patients with AF applicable to both sexes. We did not observe smaller changes in $\dot{V}O_{2peak}$ in females than males. AF severity, general health perceptions and blood pressure did not improve as much in females as males with AF following exercise training. Several outcomes (i.e., $\dot{V}O_{2peak}$, general QoL, resting HR and blood pressure, and anxiety symptoms) improved in males following exercise training when compared to usual care. Such findings were not significant in females, likely due to the small sample size. The underrepresentation of females in clinical studies continues to hinder establishing clear conclusions in sex-specific exercise research in patients with AF.

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6.9. Supplemental material

Appendix 6.1. PRISMA checklist for reporting systematic reviews

Title		
Title	1	Identify the report as a systematic review.
Abstract		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
Introduction		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
Methods		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.

Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
Results		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.

Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
Discussion		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
Other information		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

PRISMA: Preferred reporting items for systematic review and meta-analyses.

Appendix 6.2. Search strategies for all databases used for the systematic review

CINAHL (EBSCOhost)

MH "Atrial Fibrillation" OR (TI (((atrial or auricular or atrium) N3 fibril*)) OR AB (((atrial or auricular or atrium) N3 fibril*))) OR (TI ((afib or a-fib)) OR AB ((afib or a-fib))) OR (TI (((atrial or AF) W3 burden)) OR AB (((atrial or AF) W3 burden)))

((MH "Rehabilitation, Cardiac+") OR (MH "Therapeutic Exercise+") OR (MH "Movement") OR (MH "Exercise+") OR (MH "Physical Fitness") OR (MH "Physical Activity") OR ((MH "Sports") OR (MH "Aquatic Sports") OR (MH "Swimming") OR (MH "Athletic Training") OR (MH "Athletic Training Programs") OR (MH "Body Building") OR (MH "Cycling") OR (MH "Race Walking") OR (MH "Running") OR (MH "Jogging") OR (MH "Running, Distance") OR (MH "Weight Lifting") OR (MH "Martial Arts")) OR ((MH "Aerobic Dancing") OR (MH "Dancing")) OR (TI (((cardiac or cardiopulmonary or cardiovascular or heart or infarct or coronary) N3 (rehab* or conditioning))) OR AB (((cardiac or cardiovascular or heart or infarct or coronary) N3 (rehab* or conditioning)).)) OR (TI ((fitness or aerobic# or exercis*) N3 (therap* or rehab* or class* or course# or program* or training# or treatment#))) OR AB ((fitness or aerobic# or exercis*) N3 (therap* or rehab* or class* or course# or program* or training# or treatment#)))) OR (TI "continuous passive motion" OR AB "continuous passive motion") OR (TI (((movement or motion) W0 (therap* or technique# or technic#))) OR AB (((movement or motion) W0 (therap* or technique# or technic#))))) OR ((TI (((active or ballistic or dynamic or isometric or passive or relaxed or static) N2 stretch*)) OR AB (((active or ballistic or dynamic or isometric or passive or relaxed or static) N2 stretch*))) OR (TI "muscle stretching*" OR AB "muscle stretching*") OR (TI "proprioceptive neuromuscular facilitation" OR AB "proprioceptive neuromuscular facilitation") OR (TI ((PNF W0 (stretch* or exercise# or therap* or technique#))) OR

AB ((PNF W0 (stretch* or exercise# or therap* or technique#)))) OR (TI (((stretch or plyometric or isokinetic or isometric or isotonic) N3 (drill# or exercise# or train* or activit*))) OR AB (((stretch or plyometric or isokinetic or isometric or isotonic) N3 (drill# or exercise# or train* or activit*)))) OR TI exercis* OR (TI ((physical* W0 (activ* or fit* or exercis* or training# or conditioning))) OR AB ((physical* W0 (activ* or fit* or exercis* or training# or conditioning)))) OR (TI (calisthenics or callisthenics) OR AB (calisthenics or or callisthenics)) OR (TI (((interval or circuit) W0 training#)) OR AB (((interval or circuit) W0 training#))) OR (TI ((jogging or running or bike# or biking or bicycl* or cycling or swimming or dancing)) OR AB ((jogging or running or bike# or biking or bicycl* or cycling or swimming or dancing))) OR (TI ((sport# or athletic#)) OR AB ((sport# or athletic#))) OR (TI ((martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu)) OR AB ((martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu)))) OR (TI ((walk or ambulate# or ambulation)) OR AB ((walk or ambulate# or ambulation))) OR (TI (stair# N2 climb*) OR AB (stair# N2 climb*)) OR (TI (((Strength* or resistance or weight#) N3 (training# or program*))) OR AB (((Strength* or resistance or weight#) N3 (training# or program*)))) OR (TI ((muscle N2 (training# or strengthening))) OR AB ((muscle N2 (training# or strengthening)))) OR (TI ((pilates or peloton or zumba or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan)) OR AB ((pilates or zumba or peloton or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan)))

Cochrane Library (Wiley)

MeSH descriptor: [Atrial Fibrillation] this term only

((atrial or auricular or atrium) near/3 fibril*):ti,ab,kw

(afib or a-fib):ti,ab,kw

((atrial or AF) near/3 burden):ti,ab,kw

{or #1-#4}

MeSH descriptor: [Cardiac Rehabilitation] this term only

MeSH descriptor: [Rehabilitation] this term only

MeSH descriptor: [] explode all trees and with qualifier(s): [rehabilitation - RH]

MeSH descriptor: [Exercise Therapy] explode all trees

MeSH descriptor: [Movement] this term only

MeSH descriptor: [Exercise] explode all trees

MeSH descriptor: [Physical Fitness] this term only

MeSH descriptor: [Sports] this term only

MeSH descriptor: [Martial Arts] this term only

MeSH descriptor: [Bicycling] this term only

MeSH descriptor: [Weight Lifting] this term only

MeSH descriptor: [Exercise Movement Techniques] explode all trees

MeSH descriptor: [Dancing] this term only

((cardiac or cardiopulmonary or cardiovascular or heart or infarct or coronary) near/3 (rehab* or conditioning)):ti,ab,kw

rehab*:ti

((fitness or aerobic or aerobics or exercis*) near/3 (therap* or rehab* or class* or course or courses or program* or training or treatment or treatments)):ti,ab,kw

continuous passive motion:ti,ab,kw

((movement or motion) next (therap* or technique or techniques or technic or technics)):ti,ab,kw

((active or ballistic or dynamic or isometric or passive or relaxed or static) near/2 stretch*):ti,ab,kw

muscle stretching*:ti,ab,kw

proprioceptive neuromuscular facilitation:ti,ab,kw

(PNF next (stretch* or exercise or therap* or technique or techniques)):ti,ab,kw

((stretch or plyometric or isokinetic or isometric or isotonic) near/3 (drill or drills or exercise or exercises or train* or activit*)):ti,ab,kw

exercis*:ti

(physical* next (activ* or fit* or exercis* or training or trainings or conditioning)):ti,ab,kw

(calisthenics or callisthenics):ti,ab,kw

((interval or circuit) next training or trainings):ti,ab,kw

(jogging or running or bike or bikes or biked or biking or bicycl* or cycling or swimming or dancing):ti,ab,kw

(sport or sports or athletic or athletics):ti,ab,kw

(martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu):ti,ab,kw

(walk or ambulate or ambulation):ti,ab,kw

((stair or stairs) near/2 climb*):ti,ab,kw

((Strength* or resistance or weight or weights) near/3 (training or trainings or program*)):ti,ab,kw

(muscle near/2 (training or trainings or strengthening)):ti,ab,kw

(pilates or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan):ti,ab,kw

{or #6-#40}

#5 and #41

Embase (OvidSP)

atrial fibrillation/ or chronic atrial fibrillation/ or experimental atrial fibrillation/ or new-onset atrial fibrillation/ or paroxysmal atrial fibrillation/ or permanent atrial fibrillation/ or persistent atrial fibrillation/

((atrial or auricular or atrium) adj3 fibril*).tw.

(afib or a-fib).tw.

((atrial or AF) adj3 burden).tw.

or/1-4

heart rehabilitation/

exp kinesiotherapy/

movement/

exp exercise/

physical fitness/

physical activity/ or exp climbing/ or stretching/ or walking/ or weight lifting/

sport/ or body building/ or exp combat sport/ or cycling/ or jogging/ or nordic walking/ or running/ or swimming/ or yoga/

dance/

((cardiac or cardiovascular or heart or infarct or coronary) adj3 (rehab* or conditioning)).tw.

kinesiotherapy.tw.

((fitness or aerobic? or exercis*) adj3 (therap* or rehab* or class* or course? or program* or training? or treatment?)).tw.

(calisthenics or callisthenics).tw.

continuous passive motion.tw.

((movement or motion) adj (therap* or technique? or technic?)).tw.

((active or ballistic or dynamic or isometric or passive or relaxed or static) adj2 stretch*).tw.

muscle stretching*.tw.

proprioceptive neuromuscular facilitation.tw.

(PNF adj (stretch* or exercise? or therap* or technique?)).tw.

((stretch or plyometric) adj3 (drill? or exercise? or train* or activit*)).tw.

exercis*.ti.

(physical* adj (activ* or fit* or exercis* or training? or conditioning)).tw.

((circuit or interval) adj training?).tw.

(jogging or running or bike? or biking or bicycl* or swimming or dancing).tw.

(walk or walking or ambulate? or ambulation).tw.

(stair? adj2 climb*).tw.

(sport? or athletic?).tw.

(martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu).tw.

((Strength* or resistance or weight?) adj3 (training? or program*)).tw.

(muscle adj2 (training? or strengthening)).tw.

(pilates or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan).tw.

or/6-35

5 and 36

exp animals/

exp animal experimentation/

exp models animal/

exp vertebrate/

or/38-41

exp humans/ or exp human

experimentation/

42 not 43

37 not 44

MEDLINE (OvidSP)

Atrial Fibrillation/

((atrial or auricular or atrium) adj3 fibril*).tw,kf.

(afib or a-fib).tw,kf.

((atrial or AF) adj3 burden).tw,kf.

or/1-4

Cardiac Rehabilitation/

Rehabilitation/

rh.fs.

exp Exercise Therapy/

movement/

exp exercise/

physical fitness/

sport/

Martial Arts/

Bicycling/

Weight Lifting/

exp Exercise Movement Techniques/

dancing/

((cardiac or cardiopulmonary or cardiovascular or heart or infarct or coronary) adj3 (rehab* or conditioning)).tw,kf.

rehab*.ti.

((fitness or aerobic? or exercis*) adj3 (therap* or rehab* or class* or course? or program* or training? or treatment?)).tw,kf.

continuous passive motion.tw,kf.

((movement or motion) adj (therap* or technique? or technic?)).tw,kf.

((active or ballistic or dynamic or isometric or passive or relaxed or static) adj2 stretch*).tw,kf.

muscle stretching*.tw,kf.

proprioceptive neuromuscular facilitation.tw,kf.

(PNF adj (stretch* or exercise? or therap* or technique?)).tw,kf.

((stretch or plyometric or isokinetic or isometric or isotonic) adj3 (drill? or exercise? or train* or activit*)).tw,kf.

exercis*.ti.

(physical* adj (activ* or fit* or exercis* or training? or conditioning)).tw,kf.

(calisthenics or callisthenics).tw,kf.

((interval or circuit) adj training?).tw,kf.

(jogging or running or bike? or biking or bicycl* or cycling or swimming or dancing).tw,kf.

(sport? or athletic?).tw,kf.

(martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu).tw,kf.

(walk or ambulate? or ambulation).tw,kf.

(stair? adj2 climb*).tw,kf.

((Strength* or resistance or weight?) adj3 (training? or program*)).tw,kf.

(muscle adj2 (training? or strengthening)).tw,kf.

(pilates or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan).tw,kw.

or/6-40

5 and 41

exp animals/

exp animal experimentation/

exp models animal/

exp vertebrates/

or/43-46

exp humans/ or exp human experimentation/

47 not 48

42 not 49

(exp infant/ or exp child/ or adolescent/) not exp adult/

50 not 51

PycINFO (Ovid)

Fibrillation (Heart)/

Atrial Fibrillation.mh.

((atrial or auricular or atrium) adj3

fibril*).ti,ab,id.

(afib or a-fib).ti,ab,id.

((atrial or AF) adj3 burden).ti,ab,id.

or/1-5

Cardiac rehabilitation.mh.

rehabilitation/

exercise therapy.mh.

exp exercise/

movement.mh.

movement therapy/

physical fitness.mh.

Physical Fitness/

Physical Activity/

(sport or martial arts or bicycling or weight lifting or swimming or dancing or jogging or

running or walking).mh.

sports/ or martial arts/ or swimming/

Exercise Movement Techniques.mh.

dance therapy/

(rehab* or conditioning).ti,ab,id.

(fitness or aerobic? or exercis*).ti,ab,id.

(movement or motion).ti,ab,id.

stretch*.ti,ab,id.

proprioceptive neuromuscular facilitation.ti,ab,id.

(PNF adj (therap* or technique?)).ti,ab,id.

((plyometric or isokinetic or isometric or isotonic) adj3 (drill? or train* or activit*)).ti,ab,id.

(physical* adj (activ* or training? or conditioning)).ti,ab,id.

(calisthenics or callisthenics).ti,ab,id.

((interval or circuit) adj training?).ti,ab,id.

(jogging or running or bike? or biking or bicycl* or cycling or swimming or dancing).ti,ab,id.

(sport? or athletic?).ti,ab,id.

(martial arts or aikido or gong fu or gongfu or hap ki do or judo or jujitsu or karate or kung fu or tae kwon do or wushu).ti,ab,id.

(walk or ambulate? or ambulation).ti,ab,id.

(stair? adj2 climb*).ti,ab,id.

((Strength* or resistance or weight?) adj3 (training? or program*)).ti,ab,id.

(muscle adj2 (training? or strengthening)).ti,ab,id.

(pilates or yoga or ch'i kung or qi gong or qigong or tai chi or t'ai chi or ji quan or tai ji or taiji or taijiquan).ti,ab,id.

or/7-37

6 and 38

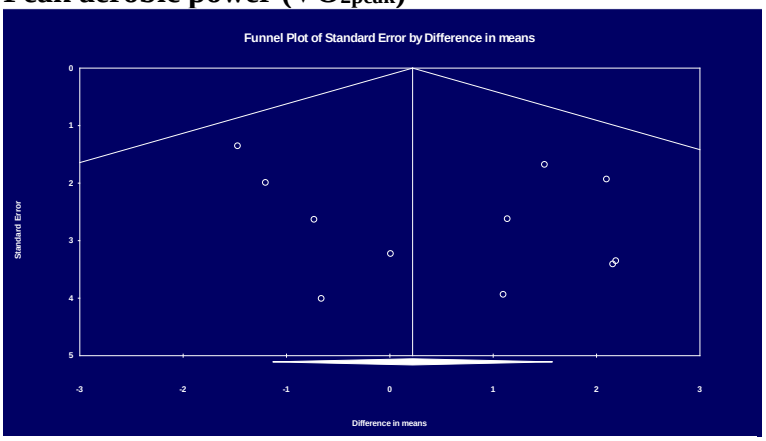
Dissertations and Theses

((TI((atrial OR auricular OR atrium) NEAR/3 fibril*) OR ab((atrial OR auricular OR atrium) NEAR/3 fibril*)) OR (TI(afib OR a-fib) OR AB(afib OR a-fib)) OR (TI((atrial OR AF) PRE/3 burden) OR AB((atrial OR AF) PRE/3 burden))) AND ((ti((rehab* OR conditioning)) OR ab((rehab* OR conditioning))) OR (ti((fitness OR aerobic OR exercis*)) OR ab((fitness OR aerobic OR exercis*))) OR (ti((movement OR motion)) OR ab((movement OR motion))) OR (ti(stretch*) OR ab(stretch*)) OR (ti("proprioceptive neuromuscular facilitation") OR ab("proprioceptive neuromuscular facilitation")) OR (TI(PNF NEAR/0 (therap* OR technique)) OR AB(PNF NEAR/0 (therap* OR technique))) OR (TI((plyometric OR isokinetic OR isometric OR isotonic) NEAR/3 (drill OR train* OR activit*)) OR AB((plyometric OR isokinetic OR isometric OR isotonic) NEAR/3 (drill OR train* OR activit*))) OR (TI(physical* NEAR/0 (activ* OR training OR conditioning)) OR AB(physical* NEAR/0 (activ* OR training OR conditioning))) OR (TI(calisthenics) OR AB(calisthenics)) OR (TI((interval OR circuit) NEAR/0 training) OR AB((interval OR circuit) NEAR/0 training)) OR (TI(jogging OR running OR bike OR biking OR bicycl* OR cycling OR swimming OR dancing) OR AB(jogging OR running OR bike OR biking OR bicycl* OR cycling OR swimming OR dancing)) OR (TI(sport OR athletic) OR AB(sport OR athletic)) OR (TI(martial arts OR aikido OR gong fu OR gongfu OR hap ki do OR judo OR jujitsu OR karate OR kung fu OR tae kwon do OR wushu) OR AB(martial arts OR aikido OR gong fu OR gongfu OR hap ki do OR judo OR jujitsu OR karate OR kung fu OR tae kwon do OR wushu)) OR (TI(walk OR ambulate OR ambulation) OR AB(walk OR ambulate OR ambulation)) OR (TI(stair NEAR/2 climb*) OR AB(stair NEAR/2 climb*)) OR (TI((Strength* OR resistance OR weight) NEAR/3 (training OR program*)) OR AB((Strength* OR resistance OR weight) NEAR/3

(training OR program*))) OR (TI(muscle NEAR/2 (training OR strengthening)) OR AB(muscle NEAR/2 (training OR strengthening))) OR (TI(pilates OR yoga OR ch'i kung OR qi gong OR qigong OR tai chi OR t'ai chi OR ji quan OR tai ji OR taiji OR taijiquan) OR AB(pilates OR yoga OR ch'i kung OR qi gong OR qigong OR tai chi OR t'ai chi OR ji quan OR tai ji OR taiji OR taijiquan)))

Appendix 6.3. Funnel plots and Egger's tests for the most relevant outcomes of the systematic review

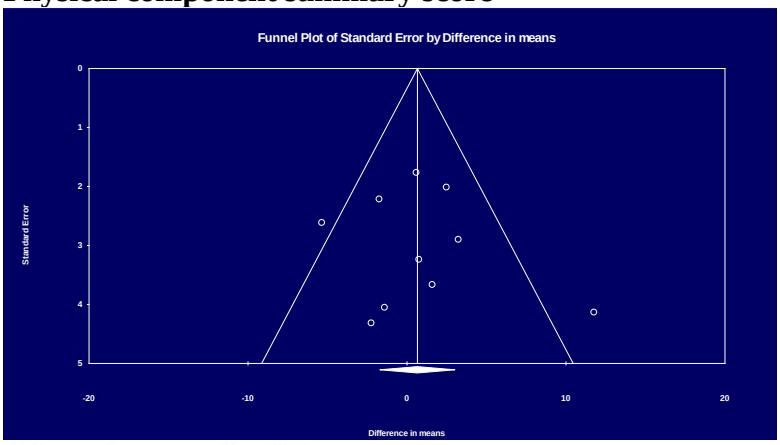
Peak aerobic power ($\dot{V}O_{2peak}$)



Egger's regression intercept

Intercept	0,65924
Standard error	0,58646
95% lower limit (2-tailed)	-0,66742
95% upper limit (2-tailed)	1,98590
t-value	1,12410
df	9,00000
P-value (1-tailed)	0,14503
P-value (2-tailed)	0,29006

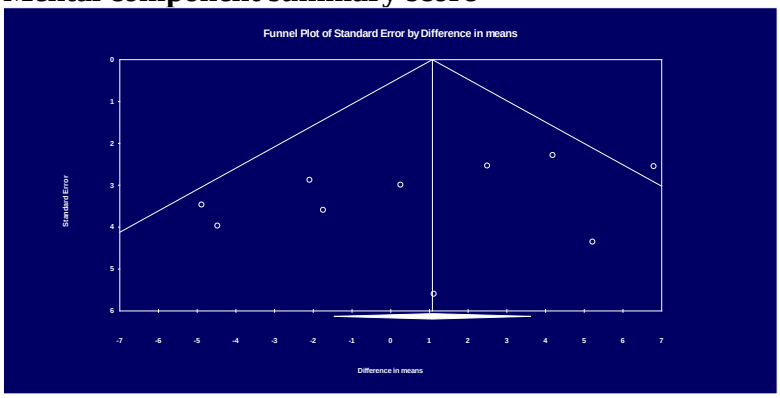
Physical component summary score



Egger's regression intercept

Intercept	0,72106
Standard error	1,47542
95% lower limit (2-tailed)	-2,68125
95% upper limit (2-tailed)	4,12337
t-value	0,48872
df	8,00000
P-value (1-tailed)	0,31908
P-value (2-tailed)	0,63816

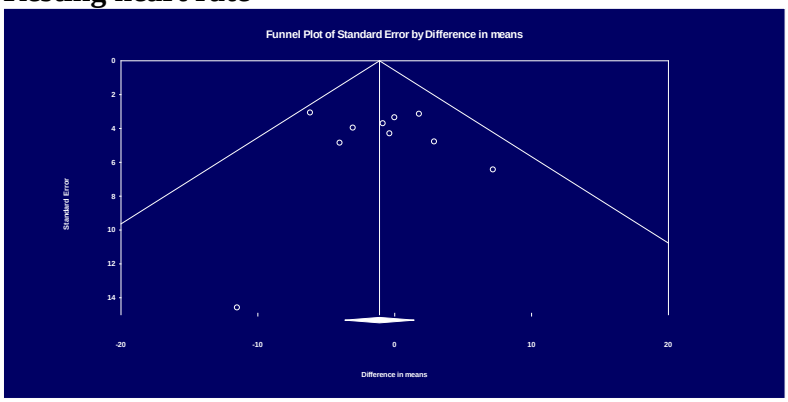
Mental component summary score



Egger's regression intercept

Intercept	-2,20499
Standard error	1,60313
95% lower limit (2-tailed)	-5,90180
95% upper limit (2-tailed)	1,49183
t-value	1,37543
df	8,00000
P-value (1-tailed)	0,10314
P-value (2-tailed)	0,20628

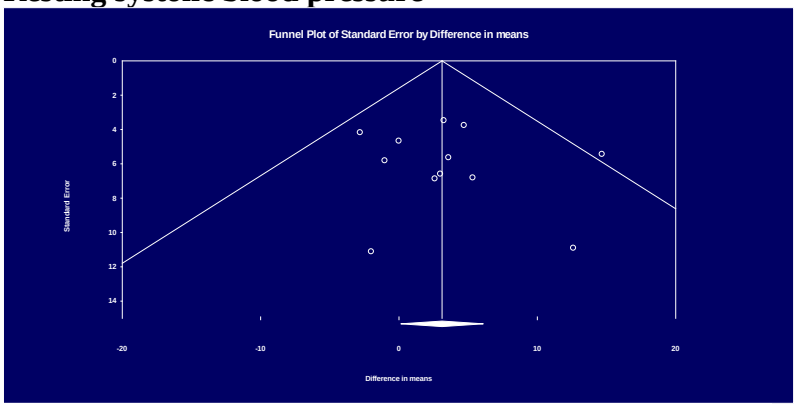
Resting heart rate



Egger's regression intercept

Intercept	0,20939
Standard error	0,97681
95% lower limit (2-tailed)	-2,04314
95% upper limit (2-tailed)	2,46192
t-value	0,21436
df	8,00000
P-value (1-tailed)	0,41781
P-value (2-tailed)	0,83563

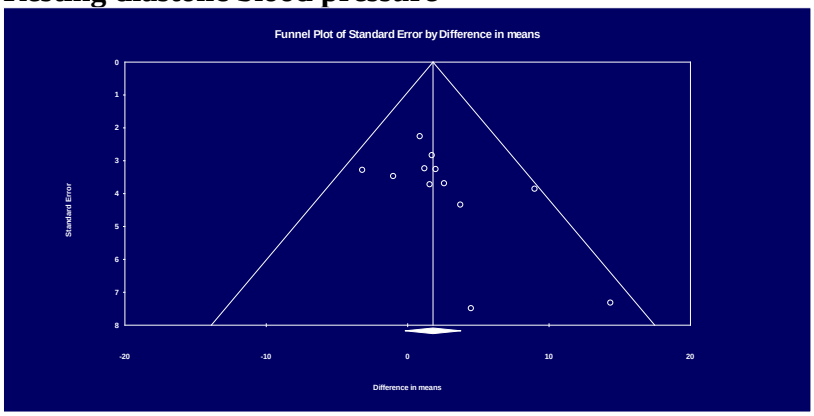
Resting systolic blood pressure



Egger's regression intercept

Intercept	0,44855
Standard error	0,84789
95% lower limit (2-tailed)	-1,44067
95% upper limit (2-tailed)	2,33777
t-value	0,52902
df	10,00000
P-value (1-tailed)	0,30417
P-value (2-tailed)	0,60833

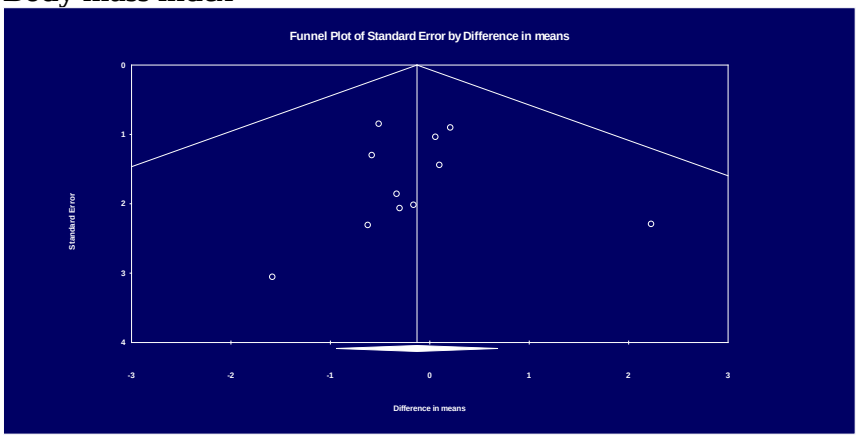
Resting diastolic blood pressure



Egger's regression intercept

Intercept	1,77757
Standard error	0,85233
95% lower limit (2-tailed)	-0,12153
95% upper limit (2-tailed)	3,67667
t-value	2,08555
df	10,00000
P-value (1-tailed)	0,03180
P-value (2-tailed)	0,06360

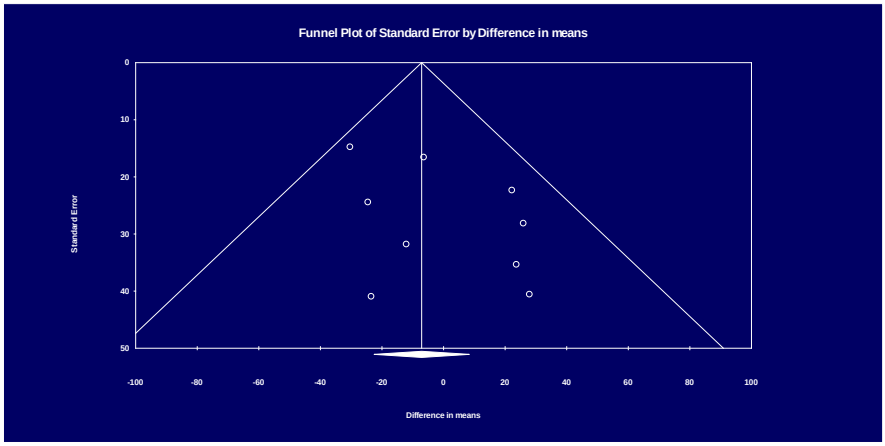
Body mass index



Egger's regression intercept

Intercept	0,03322
Standard error	0,35958
95% lower limit (2-tailed)	-0,78022
95% upper limit (2-tailed)	0,84665
t-value	0,09238
df	9,00000
P-value (1-tailed)	0,46421
P-value (2-tailed)	0,92842

Six-minute walk test



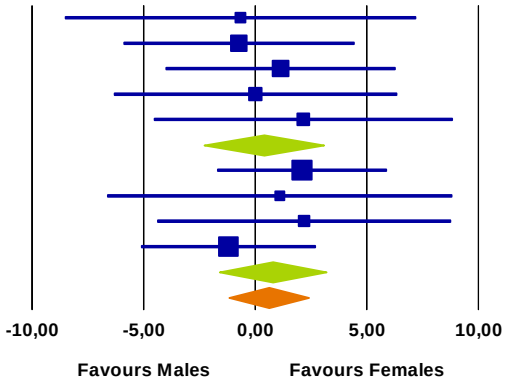
Egger's regression intercept

Intercept	1,36278
Standard error	0,88148
95% lower limit (2-tailed)	-0,72159
95% upper limit (2-tailed)	3,44715
t-value	1,54601
df	7,00000
P-value (1-tailed)	0,08301
P-value (2-tailed)	0,16602

Appendix 6.4. Subgroup analyses comparing changes in peak aerobic power ($\dot{V}O_{2peak}$) in patients with atrial fibrillation following exercise training between sexes (A to G)

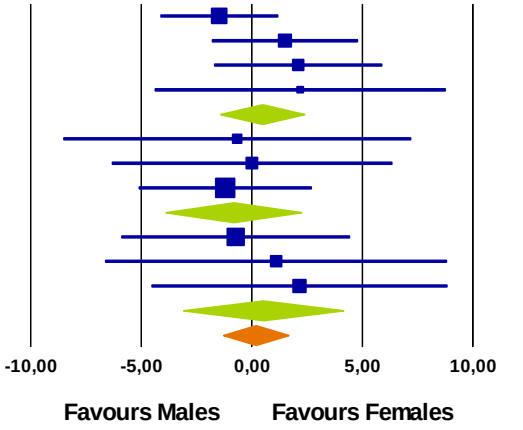
A)

Group by Frequency	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
2 days/wk	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
2 days/wk	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
2 days/wk	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
2 days/wk	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
2 days/wk	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
2 days/wk	Pooled	0,386	-2,300	3,072	0,282	0,778	36	61
3+ days/wk	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
3+ days/wk	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
3+ days/wk	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
3+ days/wk	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
3+ days/wk	Pooled	0,781	-1,612	3,174	0,640	0,522	41	94
Overall	Pooled	0,606	-1,181	2,393	0,665	0,506	77	155



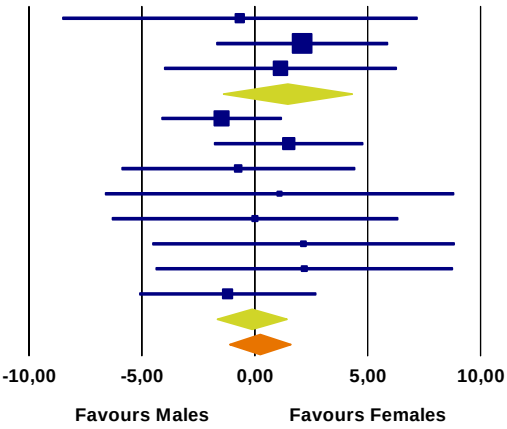
B)

Group by Intensity	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Moderate	Cai 2022 a	-1,470	-4,131	1,191	-1,083	0,279	18	32
Moderate	Cai 2022 b	1,500	-1,797	4,797	0,892	0,373	16	34
Moderate	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
Moderate	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
Moderate	Pooled	0,472	-1,426	2,370	0,487	0,626	46	91
M-to-V	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
M-to-V	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
M-to-V	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
M-to-V	Pooled	-0,835	-3,900	2,231	-0,534	0,594	41	88
Vigorous	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
Vigorous	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
Vigorous	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
Vigorous	Pooled	0,514	-3,100	4,129	0,279	0,780	17	36
Overall	Pooled	0,177	-1,296	1,651	0,236	0,814	104	215



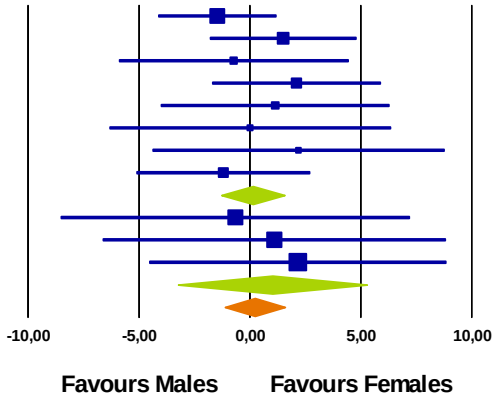
C)

Group by Duration	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
>12 wks	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
>12 wks	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
>12 wks	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
>12 wks	Pooled	1,444	-1,404	4,292	0,994	0,320	28	49
12 wks or less	Cai 2022 a	-1,470	-4,131	1,191	-1,083	0,279	18	32
12 wks or less	Cai 2022 b	1,500	-1,797	4,797	0,892	0,373	16	34
12 wks or less	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
12 wks or less	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
12 wks or less	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
12 wks or less	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
12 wks or less	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
12 wks or less	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
12 wks or less	Pooled	-0,136	-1,674	1,401	-0,174	0,862	83	172
Overall	Pooled	0,220	-1,133	1,573	0,319	0,750	111	221



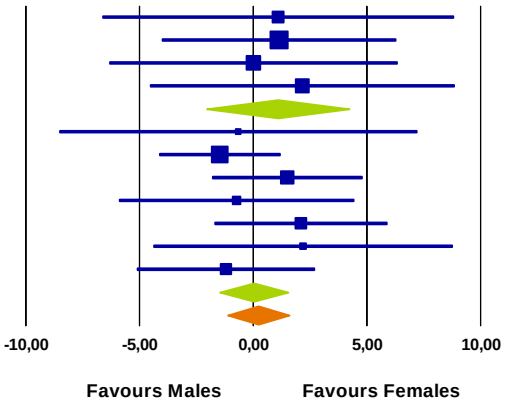
D)

Group by Interval vs. Continuous	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Continuous	Cai 2022 a	-1,470	-4,131	1,191	-1,083	0,279	18	32
Continuous	Cai 2022 b	1,500	-1,797	4,797	0,892	0,373	16	34
Continuous	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
Continuous	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
Continuous	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
Continuous	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
Continuous	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
Continuous	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
Continuous	Pooled	0,131	-1,296	1,558	0,180	0,857	90	178
Interval	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
Interval	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
Interval	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
Interval	Pooled	1,014	-3,239	5,267	0,467	0,640	21	43
Overall	Pooled	0,220	-1,133	1,573	0,319	0,750	111	221



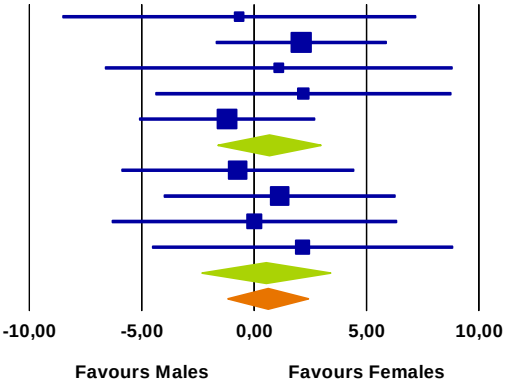
E)

Group by Intervention type	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Exercise only	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
Exercise only	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
Exercise only	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
Exercise only	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
Exercise only	Pooled	1,081	-2,054	4,215	0,676	0,499	19	32
Multi-component	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
Multi-component	Cai 2022 a	-1,470	-4,131	1,191	-1,083	0,279	18	32
Multi-component	Cai 2022 b	1,500	-1,797	4,797	0,892	0,373	16	34
Multi-component	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
Multi-component	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
Multi-component	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
Multi-component	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
Multi-component	Pooled	0,023	-1,476	1,523	0,030	0,976	92	189
Overall	Pooled	0,220	-1,133	1,573	0,319	0,750	111	221



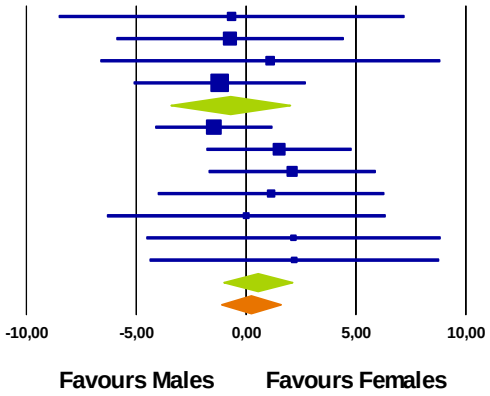
F)

Group by Setting	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Combined	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
Combined	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
Combined	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
Combined	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
Combined	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
Combined	Pooled	0,659	-1,631	2,948	0,564	0,573	54	117
Onsite	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
Onsite	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
Onsite	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
Onsite	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
Onsite	Pooled	0,524	-2,333	3,382	0,360	0,719	23	38
Overall	Pooled	0,606	-1,181	2,393	0,665	0,506	77	155



G)

Group by Baseline fitness	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
High	Bittman 2022	-0,660	-8,523	7,203	-0,165	0,869	13	23
High	Joensen 2019	-0,730	-5,898	4,438	-0,277	0,782	9	16
High	Malmo 2016	1,100	-6,624	8,824	0,279	0,780	5	10
High	Wagner 2018	-1,200	-5,112	2,712	-0,601	0,548	24	59
High	Pooled	-0,722	-3,436	1,993	-0,521	0,602	51	108
Low	Cai 2022 a	-1,470	-4,131	1,191	-1,083	0,279	18	32
Low	Cai 2022 b	1,500	-1,797	4,797	0,892	0,373	16	34
Low	Kato 2019	2,100	-1,696	5,896	1,084	0,278	8	20
Low	Okazaki 2016	1,140	-4,008	6,288	0,434	0,664	7	6
Low	Reed 2022 a	0,010	-6,324	6,344	0,003	0,998	4	6
Low	Reed 2022 b	2,160	-4,529	8,849	0,633	0,527	3	10
Low	T. Prasciene 2021	2,190	-4,387	8,767	0,653	0,514	4	5
Low	Pooled	0,532	-1,029	2,092	0,668	0,504	60	113
Overall	Pooled	0,220	-1,133	1,573	0,319	0,750	111	221



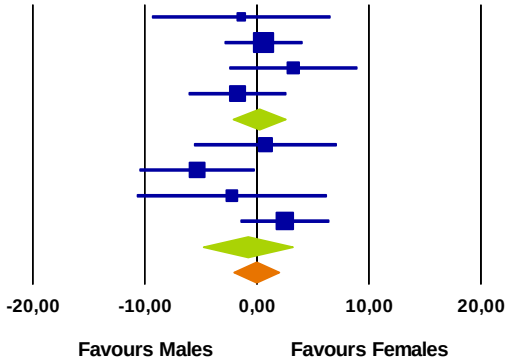
*Low: <20 mL/kg/min for females, <25 mL/kg/min for males.

Appendix 6.5. Subgroup analyses comparing changes in the physical component summary (PCS) and mental component summary (MCS) scores in patients with atrial fibrillation following exercise training between sexes (A to E)

A)

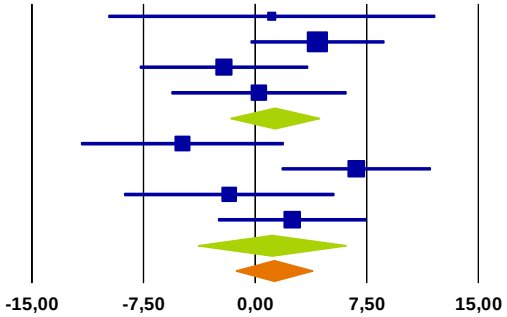
PCS (points)

Group by Frequency	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
2 days/wk	Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18
2 days/wk	Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81
2 days/wk	Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27
2 days/wk	Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28
2 days/wk	Pooled	0,202	-2,137	2,541	0,169	0,866	63	154
3+ days/wk	Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34
3+ days/wk	Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34
3+ days/wk	Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22
3+ days/wk	Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59
3+ days/wk	Pooled	-0,805	-4,791	3,182	-0,396	0,692	58	149
Overall	Pooled	-0,056	-2,074	1,962	-0,054	0,957	121	303



MCS (points)

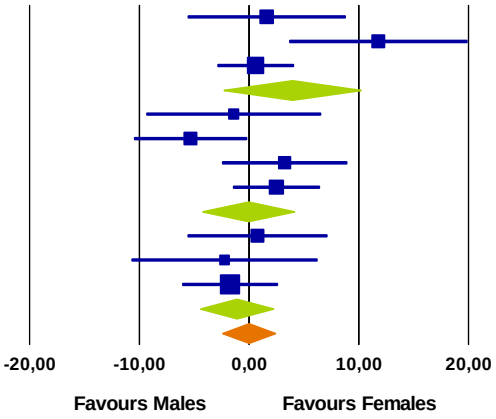
Group by Frequency	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
2 days/wk	Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18
2 days/wk	Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81
2 days/wk	Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27
2 days/wk	Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28
2 days/wk	Pooled	1,320	-1,652	4,292	0,871	0,384	61	154
3+ days/wk	Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34
3+ days/wk	Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34
3+ days/wk	Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20
3+ days/wk	Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59
3+ days/wk	Pooled	1,118	-3,836	6,072	0,442	0,658	58	147
Overall	Pooled	1,267	-1,282	3,815	0,974	0,330	119	301



B)

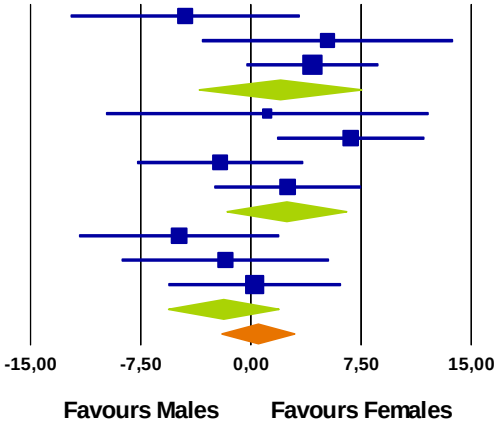
PCS (points)

Group by Intensity	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Moderate	Cai 2022 a	1,610	-5,582	8,802	0,439	0,661	18	32
Moderate	Cai 2022 b	11,780	3,671	19,889	2,847	0,004	16	34
Moderate	Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81
Moderate	Pooled	3,920	-2,313	10,153	1,233	0,218	58	147
M-to-V	Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18
M-to-V	Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34
M-to-V	Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27
M-to-V	Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59
M-to-V	Pooled	-0,071	-4,246	4,104	-0,033	0,973	65	138
Vigorous	Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34
Vigorous	Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22
Vigorous	Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28
Vigorous	Pooled	-1,130	-4,435	2,175	-0,670	0,503	32	84
Overall	Pooled	-0,038	-2,431	2,355	-0,031	0,975	155	369



MCS (points)

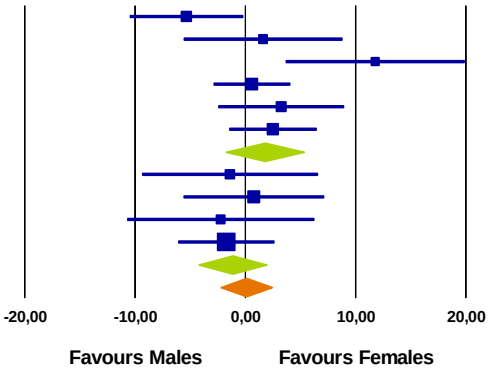
Group by Intensity	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Moderate	Cai 2022 a	-4,470	-12,254	3,314	-1,125	0,260	18	32
Moderate	Cai 2022 b	5,220	-3,315	13,755	1,199	0,231	16	34
Moderate	Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81
Moderate	Pooled	1,983	-3,545	7,512	0,703	0,482	56	147
M-to-V	Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18
M-to-V	Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34
M-to-V	Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27
M-to-V	Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59
M-to-V	Pooled	2,416	-1,652	6,484	1,164	0,244	65	138
Vigorous	Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34
Vigorous	Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20
Vigorous	Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28
Vigorous	Pooled	-1,879	-5,636	1,879	-0,980	0,327	32	82
Overall	Pooled	0,475	-1,995	2,944	0,377	0,706	153	367



C)

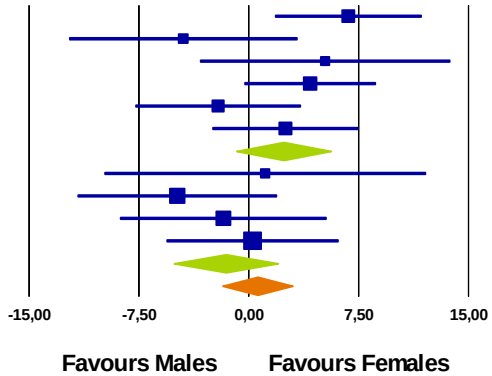
PCS (points)

Group by Interval vs. Continuous	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Continuous	Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34
Continuous	Cai 2022 a	1,610	-5,582	8,802	0,439	0,661	18	32
Continuous	Cai 2022 b	11,780	3,671	19,889	2,847	0,004	16	34
Continuous	Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81
Continuous	Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27
Continuous	Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59
Continuous	Pooled	1,768	-1,768	5,304	0,980	0,327	112	267
Interval	Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18
Interval	Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34
Interval	Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22
Interval	Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28
Interval	Pooled	-1,168	-4,220	1,883	-0,750	0,453	43	102
Overall	Pooled	0,085	-2,225	2,395	0,072	0,942	155	369



MCS (points)

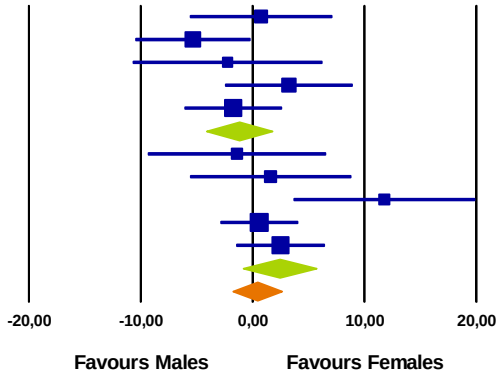
Group by Interval vs. Continuous	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Continuous	Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34
Continuous	Cai 2022 a	-4,470	-12,254	3,314	-1,125	0,260	18	32
Continuous	Cai 2022 b	5,220	-3,315	13,755	1,199	0,231	16	34
Continuous	Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81
Continuous	Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27
Continuous	Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59
Continuous	Pooled	2,372	-0,855	5,599	1,441	0,150	110	267
Interval	Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18
Interval	Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34
Interval	Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20
Interval	Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28
Interval	Pooled	-1,564	-5,119	1,991	-0,862	0,388	43	100
Overall	Pooled	0,594	-1,796	2,983	0,487	0,626	153	367



D)

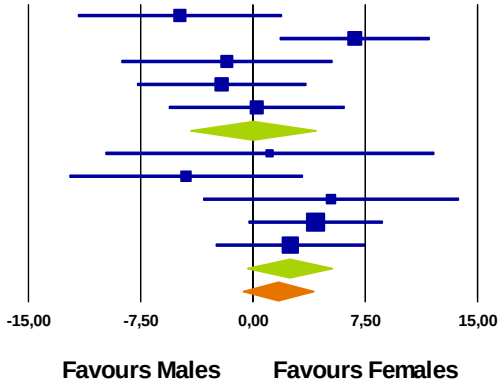
PCS (points)

Group by Intervention type	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Exercise only	Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34
Exercise only	Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34
Exercise only	Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22
Exercise only	Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27
Exercise only	Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28
Exercise only	Pooled	-1,203	-4,146	1,741	-0,801	0,423	62	145
Multi-component	Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18
Multi-component	Cai 2022 a	1,610	-5,582	8,802	0,439	0,661	18	32
Multi-component	Cai 2022 b	11,780	3,671	19,889	2,847	0,004	16	34
Multi-component	Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81
Multi-component	Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59
Multi-component	Pooled	2,412	-0,863	5,687	1,444	0,149	93	224
Overall	Pooled	0,413	-1,776	2,602	0,370	0,712	155	369



MCS (points)

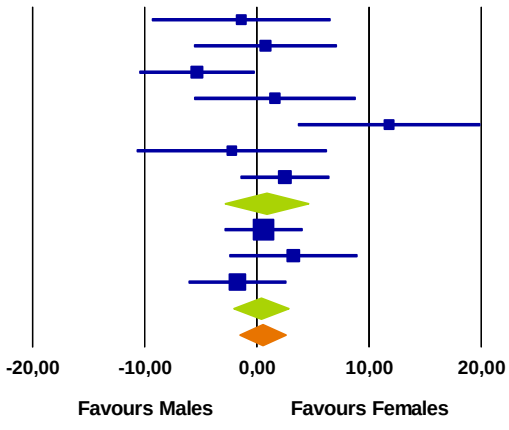
Group by Intervention type	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Exercise only	Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34
Exercise only	Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34
Exercise only	Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20
Exercise only	Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27
Exercise only	Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28
Exercise only	Pooled	-0,004	-4,185	4,178	-0,002	0,999	62	143
Multi-component	Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18
Multi-component	Cai 2022 a	-4,470	-12,254	3,314	-1,125	0,260	18	32
Multi-component	Cai 2022 b	5,220	-3,315	13,755	1,199	0,231	16	34
Multi-component	Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81
Multi-component	Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59
Multi-component	Pooled	2,443	-0,385	5,271	1,693	0,090	91	224
Overall	Pooled	1,675	-0,667	4,018	1,402	0,161	153	367



E)

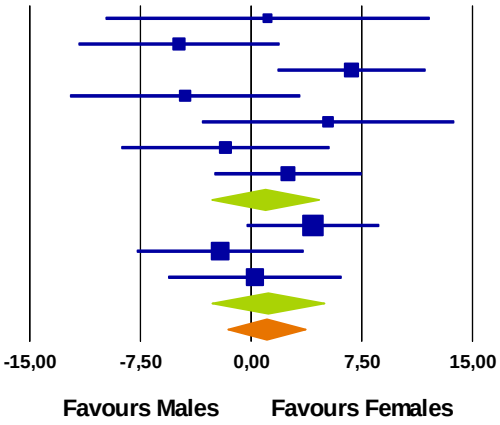
PCS (points)

Group by Setting	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Combined	Bittman 2022	-1,390	-9,339	6,559	-0,343	0,732	11	18
Combined	Borland 2020 a	0,770	-5,585	7,125	0,237	0,812	12	34
Combined	Borland 2020 b	-5,340	-10,470	-0,210	-2,040	0,041	16	34
Combined	Cai 2022 a	1,610	-5,582	8,802	0,439	0,661	18	32
Combined	Cai 2022 b	11,780	3,671	19,889	2,847	0,004	16	34
Combined	Malmo 2016	-2,230	-10,697	6,237	-0,516	0,606	6	22
Combined	Wagner 2018	2,500	-1,455	6,455	1,239	0,215	24	59
Combined	Pooled	0,856	-2,853	4,564	0,452	0,651	103	233
Onsite	Nguyen 2020	0,600	-2,867	4,067	0,339	0,734	24	81
Onsite	Reed 2022 a	3,250	-2,440	8,940	1,119	0,263	14	27
Onsite	Reed 2022 b	-1,730	-6,080	2,620	-0,779	0,436	14	28
Onsite	Pooled	0,353	-2,095	2,800	0,282	0,778	52	136
Overall	Pooled	0,505	-1,537	2,548	0,485	0,628	155	369



MCS (points)

Group by Setting	Study name	Statistics for each study					Sample size	
		Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Females	Males
Combined	Bittman 2022	1,120	-9,854	12,094	0,200	0,841	11	18
Combined	Borland 2020 a	-4,880	-11,678	1,918	-1,407	0,159	12	34
Combined	Borland 2020 b	6,800	1,798	11,802	2,665	0,008	16	34
Combined	Cai 2022 a	-4,470	-12,254	3,314	-1,125	0,260	18	32
Combined	Cai 2022 b	5,220	-3,315	13,755	1,199	0,231	16	34
Combined	Malmo 2016	-1,740	-8,787	5,307	-0,484	0,628	6	20
Combined	Wagner 2018	2,500	-2,473	7,473	0,985	0,325	24	59
Combined	Pooled	0,952	-2,677	4,580	0,514	0,607	103	231
Onsite	Nguyen 2020	4,190	-0,292	8,672	1,832	0,067	22	81
Onsite	Reed 2022 a	-2,090	-7,733	3,553	-0,726	0,468	14	27
Onsite	Reed 2022 b	0,260	-5,607	6,127	0,087	0,931	14	28
Onsite	Pooled	1,138	-2,662	4,937	0,587	0,557	50	136
Overall	Pooled	1,040	-1,584	3,665	0,777	0,437	153	367

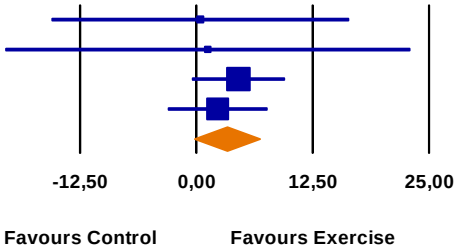


Appendix 6.6. Meta-analyses comparing changes in secondary outcomes, including the SF-36 subscales, following exercise training when compared to usual care in females with atrial fibrillation (A to O)

A)

Physical component summary score (points) - Females

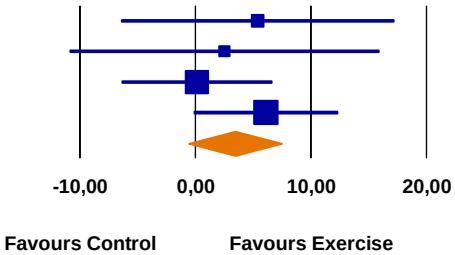
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	0,430	-15,533	16,393	0,053	0,958	11	3
Malmo 2016	1,240	-20,503	22,983	0,112	0,911	6	3
Nguyen 2020	4,530	-0,446	9,506	1,784	0,074	24	21
Wagner 2018	2,300	-3,036	7,636	0,845	0,398	24	26
Pooled	3,287	-0,215	6,789	1,840	0,066	65	53



B)

Mental component summary score (points) - Females

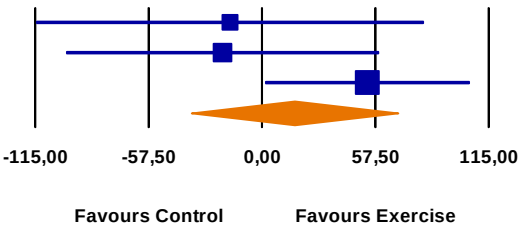
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	5,400	-6,414	17,214	0,896	0,370	11	17
Malmo 2016	2,520	-10,877	15,917	0,369	0,712	6	3
Nguyen 2020	0,140	-6,371	6,651	0,042	0,966	24	21
Wagner 2018	6,100	-0,132	12,332	1,919	0,055	24	26
Pooled	3,433	-0,580	7,447	1,677	0,094	65	67



C)

Six-minute walk test distance (metres) - Females

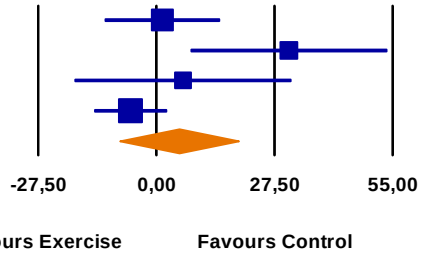
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Joensen 2019	-16,170	-114,420	82,080	-0,323	0,747	9	7
Kato 2019	-20,000	-99,226	59,226	-0,495	0,621	8	3
Wagner 2018	53,500	1,688	105,312	2,024	0,043	24	26
Pooled	16,513	-35,908	68,934	0,617	0,537	41	36



D)

Systolic blood pressure (mmHg) - Females

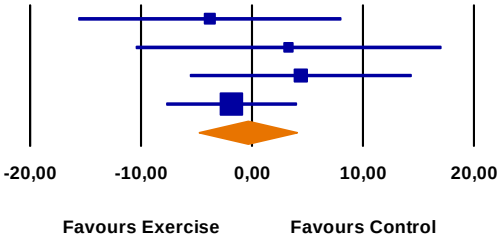
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	1,400	-11,983	14,783	0,205	0,838	11	17
Joensen 2019	30,860	8,017	53,703	2,648	0,008	9	7
Malmo 2016	6,200	-19,007	31,407	0,482	0,630	6	3
Nguyen 2020	-6,000	-14,440	2,440	-1,393	0,164	25	27
Pooled	5,279	-8,547	19,106	0,748	0,454	51	54



E)

Diastolic blood pressure (mmHg) - Females

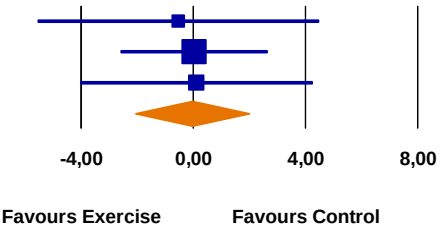
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	-3,800	-15,639	8,039	-0,629	0,529	11	17
Joensen 2019	3,300	-10,456	17,056	0,470	0,638	9	7
Malmo 2016	4,400	-5,578	14,378	0,864	0,387	6	3
Nguyen 2020	-1,850	-7,715	4,015	-0,618	0,536	25	27
Pooled	-0,374	-4,779	4,031	-0,166	0,868	51	54



F)

Body mass index (kg/m2) - Females

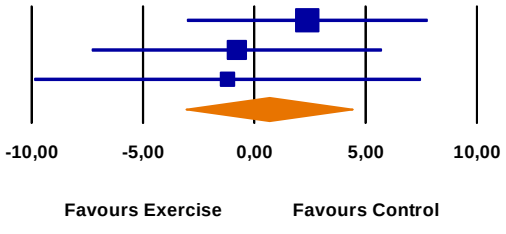
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	-0,530	-5,538	4,478	-0,207	0,836	13	17
Nguyen 2020	0,030	-2,586	2,646	0,022	0,982	25	25
Okazaki 2016	0,110	-4,028	4,248	0,052	0,958	6	5
Pooled	-0,042	-2,065	1,981	-0,041	0,967	44	47



G)

Anxiety (points) - Females

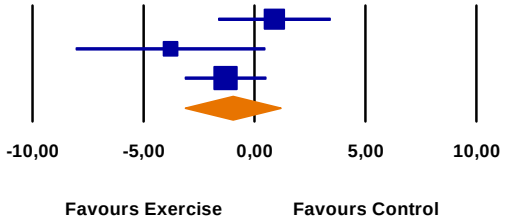
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Dalal 2019	2,380	-3,012	7,772	0,865	0,387	9	8
Lang 2018	-0,780	-7,288	5,728	-0,235	0,814	8	4
Wagner 2018	-1,200	-9,875	7,475	-0,271	0,786	24	26
Pooled	0,666	-3,079	4,411	0,349	0,727	41	38



H)

Depression (points) - Females

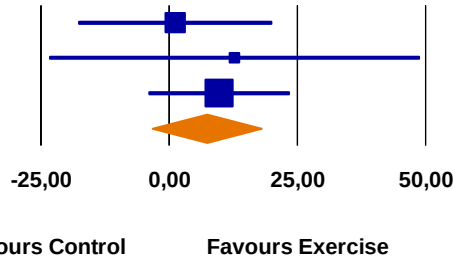
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Dalal 2019	0,900	-1,624	3,424	0,699	0,485	8	8
Lang 2018	-3,780	-8,042	0,482	-1,738	0,082	6	4
Wagner 2018	-1,300	-3,128	0,528	-1,394	0,163	24	26
Pooled	-0,983	-3,134	1,168	-0,896	0,370	38	38



I)

Physical function SF-36 (points) - Females

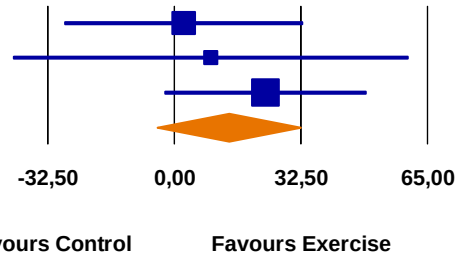
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	1,200	-17,673	20,073	0,125	0,901
Malmo 2016	12,740	-23,341	48,821	0,692	0,489
Nguyen 2020	9,750	-3,971	23,471	1,393	0,164
Pooled	7,308	-3,300	17,915	1,350	0,177



J)

Role physical SF-36 (points) - Females

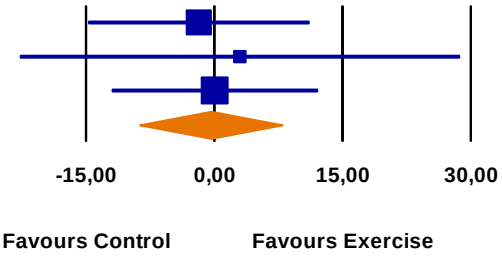
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	2,400	-28,204	33,004	0,154	0,878
Malmo 2016	9,370	-41,354	60,094	0,362	0,717
Nguyen 2020	23,420	-2,461	49,301	1,774	0,076
Pooled	13,959	-4,455	32,372	1,486	0,137



K)

General health SF-36 (points) - Females

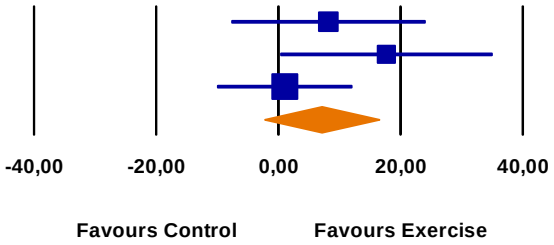
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	-1,800	-14,708	11,108	-0,273	0,785
Malmo 2016	3,000	-22,713	28,713	0,229	0,819
Nguyen 2020	0,060	-11,958	12,078	0,010	0,992
Pooled	-0,405	-8,728	7,917	-0,095	0,924



L)

Vitality SF-36 (points) - Females

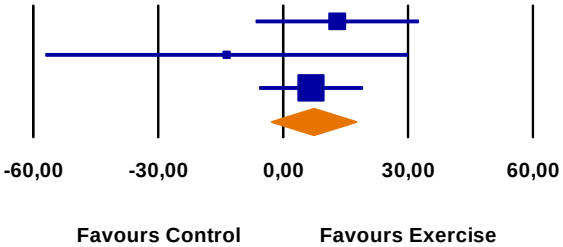
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	8,200	-7,668	24,068	1,013	0,311
Malmo 2016	17,700	0,338	35,062	1,998	0,046
Nguyen 2020	1,050	-9,995	12,095	0,186	0,852
Pooled	7,077	-2,288	16,441	1,481	0,139



M)

Social function SF-36 (points) - Females

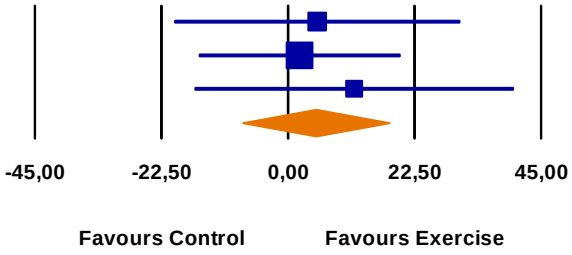
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	13,000	-6,550	32,550	1,303	0,192
Malmo 2016	-13,540	-57,047	29,967	-0,610	0,542
Nguyen 2020	6,710	-5,690	19,110	1,061	0,289
Pooled	7,307	-2,874	17,488	1,407	0,160



N)

Role emotional SF-36 (points) - Females

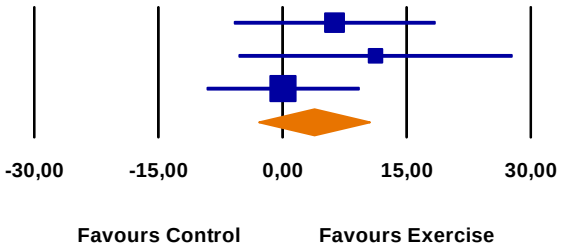
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	5,200	-20,181	30,581	0,402	0,688
Malmo 2016	2,080	-15,823	19,983	0,228	0,820
Nguyen 2020	11,770	-16,587	40,127	0,814	0,416
Pooled	4,936	-8,066	17,937	0,744	0,457



O)

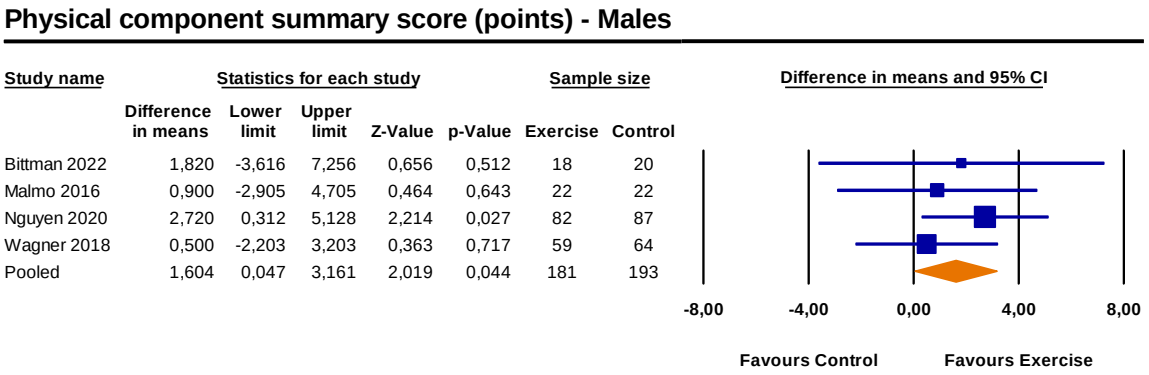
Mental health SF-36 (points) - Females

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	6,300	-5,847	18,447	1,017	0,309
Malmo 2016	11,250	-5,273	27,773	1,334	0,182
Nguyen 2020	0,070	-9,145	9,285	0,015	0,988
Pooled	3,814	-2,895	10,523	1,114	0,265

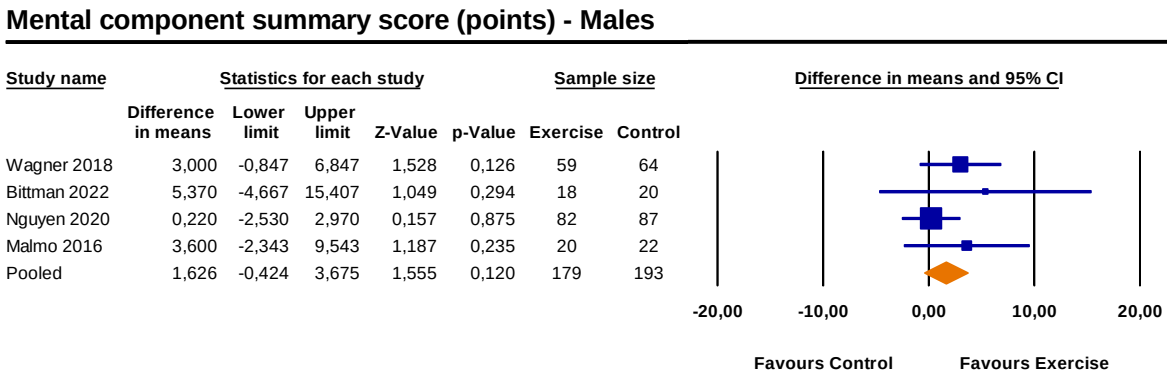


Appendix 6.7. Meta-analyses comparing changes in secondary outcomes, including the SF-36 subscales, following exercise training when compared to usual care in males with atrial fibrillation (A to Q)

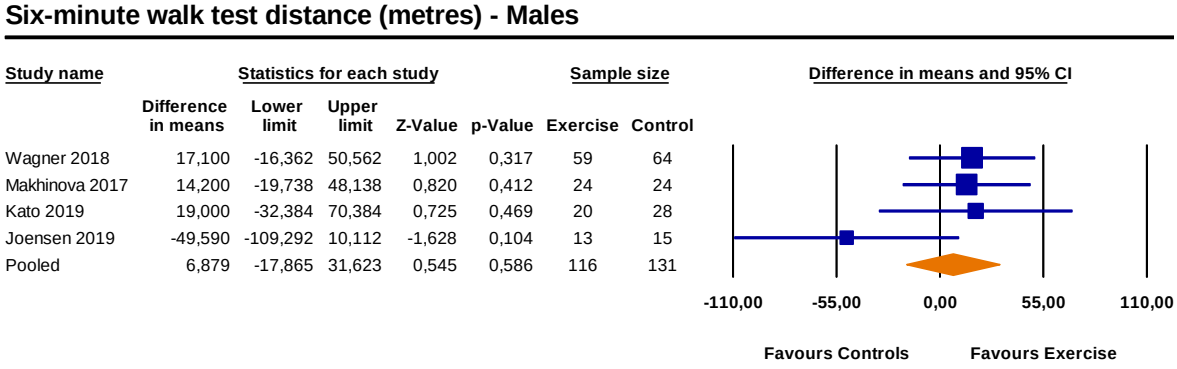
A)



B)



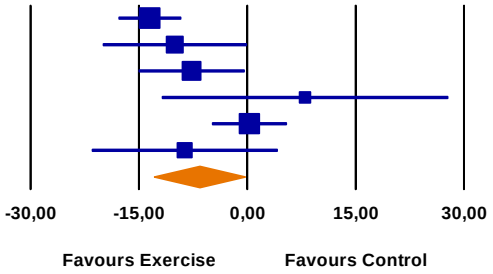
C)



D)

Resting heart rate (bpm) - Males

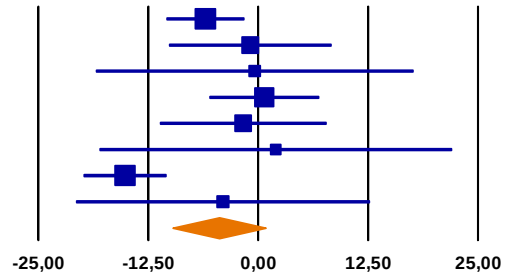
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Alves 2022	-13,500	-17,813	-9,187	-6,134	0,000	13	13
Joensen 2019	-10,020	-19,979	-0,061	-1,972	0,049	16	16
Makhinova 2017	-7,700	-15,018	-0,382	-2,062	0,039	24	24
Melo 2019	8,000	-11,808	27,808	0,792	0,429	5	6
Nguyen 2020	0,300	-4,864	5,464	0,114	0,909	94	99
Okazaki 2016	-8,650	-21,500	4,200	-1,319	0,187	6	24
Pooled	-6,620	-12,894	-0,345	-2,068	0,039	158	182



E)

Systolic blood pressure (mmHg) - Males

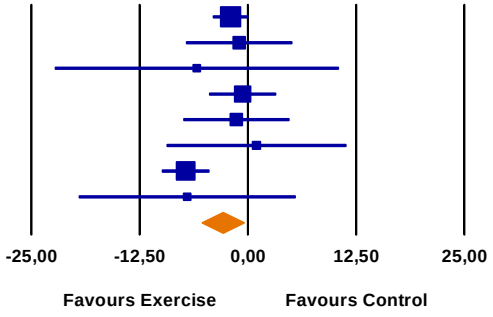
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Alves 2022	-6,000	-10,416	-1,584	-2,663	0,008	13	13
Bittman 2022	-0,900	-10,126	8,326	-0,191	0,848	21	21
Joensen 2019	-0,400	-18,440	17,640	-0,043	0,965	16	15
Makhinova 2017	0,700	-5,539	6,939	0,220	0,826	24	24
Malmo 2016	-1,700	-11,163	7,763	-0,352	0,725	20	22
Melo 2019	2,000	-18,036	22,036	0,196	0,845	5	6
Nguyen 2020	-15,140	-19,846	-10,434	-6,305	0,000	94	99
Okazaki 2016	-4,000	-20,703	12,703	-0,469	0,639	6	24
Pooled	-4,446	-9,731	0,838	-1,649	0,099	199	224



F)

Diastolic blood pressure (mmHg) - Males

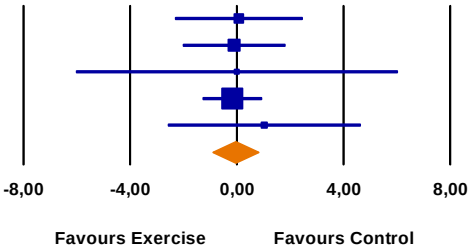
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Alves 2022	-2,000	-4,034	0,034	-1,927	0,054	13	13
Bittman 2022	-1,000	-7,126	5,126	-0,320	0,749	23	21
Joensen 2019	-5,890	-22,279	10,499	-0,704	0,481	16	15
Makhinova 2017	-0,600	-4,456	3,256	-0,305	0,760	24	24
Malmo 2016	-1,330	-7,430	4,770	-0,427	0,669	20	22
Melo 2019	1,000	-9,369	11,369	0,189	0,850	5	6
Nguyen 2020	-7,180	-9,908	-4,452	-5,158	0,000	94	99
Okazaki 2016	-7,000	-19,513	5,513	-1,096	0,273	6	24
Pooled	-2,893	-5,306	-0,479	-2,349	0,019	201	224



G)

Body mass index (kg/m2) - Males

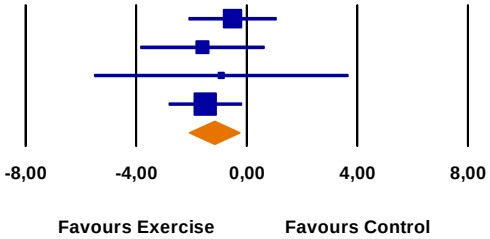
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Bittman 2022	0,080	-2,310	2,470	0,066	0,948	22	21
Makhinova 2017	-0,100	-2,022	1,822	-0,102	0,919	24	24
Melo 2019	0,000	-6,024	6,024	0,000	1,000	5	6
Nguyen 2020	-0,170	-1,278	0,938	-0,301	0,764	94	98
Okazaki 2016	1,030	-2,581	4,641	0,559	0,576	6	24
Pooled	-0,053	-0,909	0,803	-0,122	0,903	151	173



H)

Anxiety (points) - Males

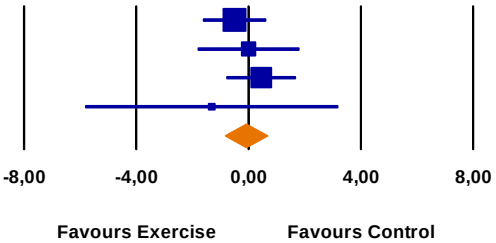
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Dalal 2019	-0,510	-2,100	1,080	-0,628	0,530	52	40
Makhinova 2017	-1,600	-3,843	0,643	-1,398	0,162	24	24
Melo 2019	-0,920	-5,514	3,674	-0,393	0,695	5	7
Wagner 2018	-1,500	-2,816	-0,184	-2,233	0,026	59	64
Pooled	-1,173	-2,079	-0,267	-2,537	0,011	140	135



I)

Depression (points) - Males

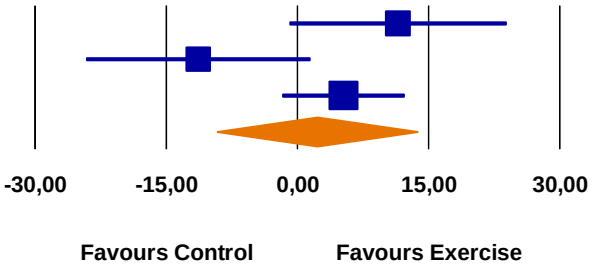
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Exercise	Control
Wagner 2018	-0,500	-1,621	0,621	-0,874	0,382	59	64
Makhinova 2017	0,000	-1,805	1,805	0,000	1,000	24	24
Dalal 2019	0,450	-0,785	1,685	0,714	0,475	52	40
Melo 2019	-1,310	-5,813	3,193	-0,570	0,569	5	7
Pooled	-0,093	-0,837	0,651	-0,244	0,807	140	135



J)

Physical function SF-36 (points) - Males

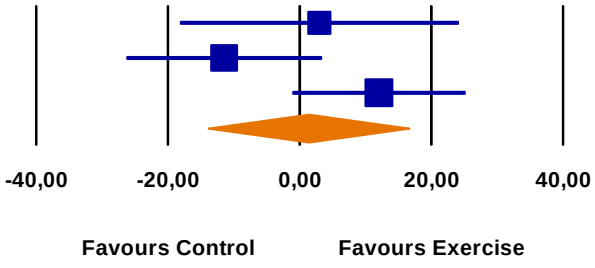
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	11,500	-0,890	23,890	1,819	0,069
Malmo 2016	-11,330	-24,138	1,478	-1,734	0,083
Nguyen 2020	5,270	-1,713	12,253	1,479	0,139
Pooled	2,245	-9,187	13,677	0,385	0,700



K)

Role physical SF-36 (points) - Males

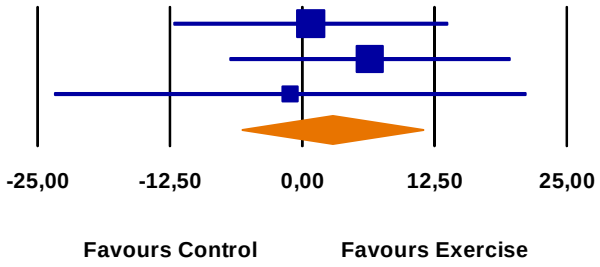
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	3,000	-18,139	24,139	0,278	0,781
Malmo 2016	-11,440	-26,257	3,377	-1,513	0,130
Nguyen 2020	12,050	-1,062	25,162	1,801	0,072
Pooled	1,341	-13,887	16,569	0,173	0,863



L)

Bodily pain SF-36 (points) - Males

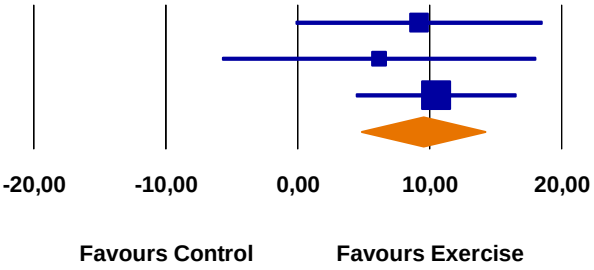
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	0,800	-12,144	13,744	0,121	0,904
Malmo 2016	6,390	-6,863	19,643	0,945	0,345
Nguyen 2020	-1,138	-23,418	21,142	-0,100	0,920
Pooled	2,842	-5,709	11,392	0,651	0,515



M)

General health SF-36 (points) - Males

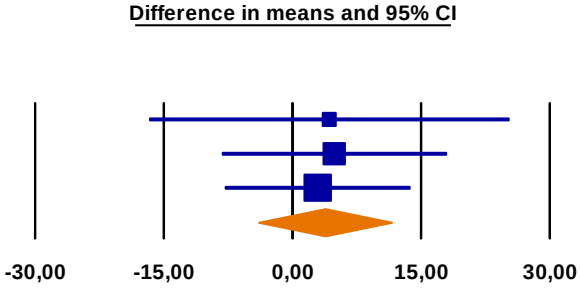
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	9,200	-0,136	18,536	1,931	0,053
Malmo 2016	6,170	-5,719	18,059	1,017	0,309
Nguyen 2020	10,490	4,418	16,562	3,386	0,001
Pooled	9,497	4,817	14,176	3,978	0,000



N)

Role emotional SF-36 (points) - Males

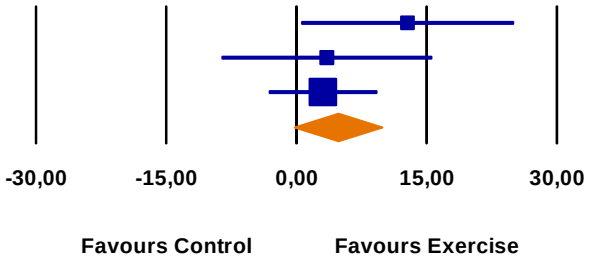
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	4,300	-16,677	25,277	0,402	0,688
Malmo 2016	4,880	-8,210	17,970	0,731	0,465
Nguyen 2020	2,940	-7,859	13,739	0,534	0,594
Pooled	3,804	-3,938	11,546	0,963	0,336



O)

Social function SF-36 (points) - Males

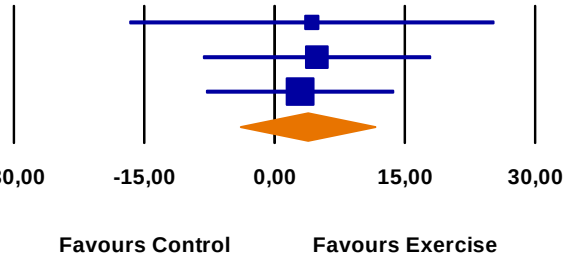
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	12,800	0,577	25,023	2,052	0,040
Malmo 2016	3,510	-8,603	15,623	0,568	0,570
Nguyen 2020	3,060	-3,162	9,282	0,964	0,335
Pooled	4,795	-0,247	9,837	1,864	0,062



P)

Role emotional SF-36 (points) - Males

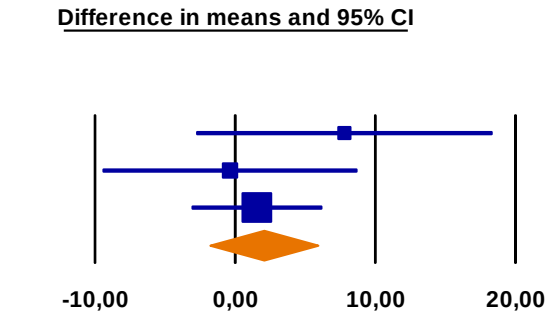
Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	4,300	-16,677	25,277	0,402	0,688
Malmo 2016	4,880	-8,210	17,970	0,731	0,465
Nguyen 2020	2,940	-7,859	13,739	0,534	0,594
Pooled	3,804	-3,938	11,546	0,963	0,336



Q)

Mental health SF-36 (points) - Males

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Bittman 2022	7,800	-2,752	18,352	1,449	0,147
Malmo 2016	-0,370	-9,437	8,697	-0,080	0,936
Nguyen 2020	1,560	-3,084	6,204	0,658	0,510
Pooled	2,042	-1,806	5,891	1,040	0,298



CHAPTER 7 - Discussion and general conclusions of the dissertation

7.1. Summary of dissertation findings

Study 1: Sex-based analyses of the short-term effects and acute responses to exercise in patients with symptomatic non-permanent atrial fibrillation

Patients feel uninformed about their symptoms and report fear of exercise-induced AF symptoms as a barrier to exercise participation.[1–3] Considering these patient concerns, a randomized crossover study was designed and performed to examine sex differences in potential short-term changes in the severity of AF symptoms during one week of high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT), when compared to one week of non-exercise Control (Chapter 3). The target population was patients with non-permanent AF (i.e., paroxysmal and persistent), as they have been shown to be more symptomatic than those with permanent AF.[4] The acute physiological and psychosocial responses to HIIT and MICT were described by sex, to inform patients and healthcare professionals of the typical exercise responses in those with AF. Seventeen participants (35% females) enrolled in the Acute-AF study. Contrary to our hypothesis, no differences in the overall symptom severity, or in the severity of most individual symptoms, were observed across the three study conditions (i.e., week of HIIT, MICT, Control) or between sexes. We found that patient palpitation severity was lower during a week of HIIT than Control rest in females, but not in males. Visual inspection of the physiological and psychosocial responses to HIIT and MICT did not reveal major differences between sexes or exercise paradigms. Females and males reported similar enjoyment following HIIT and MICT, yet only HIIT led to acute reductions in anxiety. Patients who feel uninformed and hesitant about what to expect while exercising with this disabling cardiac arrhythmia, and their healthcare providers, may appreciate the descriptive findings from Study 1. Once the

short-term effects and acute responses to exercise were examined with a sex lens, the subsequent step was to thoroughly compare the health profile between sexes, to identify which modifiable cardiovascular disease (CVD) risk factors may need to be targeted by therapeutic interventions in each sex. This need was the rationale for Study 2.

Study 2: Sex differences on physical and mental health characteristics in patients with persistent and permanent atrial fibrillation

Emerging evidence suggests a higher risk for stroke,[5,6] hospitalization[7] and mortality[8] in females than males with AF. Females' worse prognosis may derive from a poorer health profile and health behaviours than their male counterparts. Yet, there is a scarcity of sex-based analyses in health research in patients with AF. Potential sex differences in physical and mental health characteristics, and physical activity levels were examined in patients with persistent and permanent AF (Chapter 4). Using a cross-sectional design, baseline data from two randomized controlled trials (RCTs) were used to improve our understanding of sex differences in the health profile of females and males with AF. Since a higher peak aerobic power ($\dot{V}O_{2peak}$) has been shown to predict a lower risk for AF recurrence and mortality,[9] $\dot{V}O_{2peak}$ was the primary measure of interest. An equal number of females and males with persistent and permanent AF (N=78) were included to enable appropriately powered sex-based analyses. Study 2 revealed several sex differences, including a 27% lower $\dot{V}O_{2peak}$ in females than males, which was no longer significantly different between sexes after adjusting for fat-free mass. A greater proportion of females reported palpitations; they also reported better general health and had a higher resting heart rate (HR) and body fat than males. These cross-sectional findings identified several concerning health characteristics that should be preferentially targeted by treatments in females with AF. Several CVD risk factors including poor $\dot{V}O_{2peak}$, obesity, high-risk waist circumference, and low levels of moderate- to vigorous-intensity physical activity (MVPA) were highly prevalent in both sexes,

highlighting a need for lifestyle strategies. Further, $\dot{V}O_{2peak}$ and MVPA levels showed strong positive associations with several health characteristics, including general quality of life (QoL) and functional capacity. As several sex differences in symptoms and physical health were identified in Study 2, the question remained whether exercise training, a lifestyle-based therapy which has been shown to improve CVD risk factors,[10–12] may lead to improvements in these outcomes in a sex-specific manner. This research question was examined in Study 3.

Study 3: Sex-based analyses of the chronic effects of exercise training in patients with persistent and permanent atrial fibrillation

The notable clinical sex differences identified in patients with AF warrants the consideration of sex when examining the efficacy and effectiveness of exercise programs. Unfortunately, this is rarely conducted.[13–15] Following the sex-based comparison of patients' health profile, this study examined potential sex differences on the chronic effects of exercise training on physical and mental health outcomes, and physical activity levels in patients with persistent and permanent AF (Chapter 5). Data from two RCTs were leveraged to maximize the sample size for the sex-based analyses. The target population was patients with persistent and permanent AF. Since these patients typically have a worse CVD risk factor profile and more advanced cardiac remodelling than patients with paroxysmal AF,[4] they may be in the greatest need for improved quality of care and may benefit the most from exercise training. Given its prognostic value, $\dot{V}O_{2peak}$ was the primary outcome.[9] A total of 34 females and 77 males were included in Study 3. Participants engaged in supervised biweekly 23-minute HIIT or 60-minute MICT for 12 weeks. Study 3 revealed several key findings: improvements in $\dot{V}O_{2peak}$ and several physical and mental health outcomes following an exercise program did not differ by sex, supporting the benefits of aerobic exercise training for both sexes. Twelve weeks of exercise training in the form of HIIT or MICT led to $\dot{V}O_{2peak}$ improvements in females (+2.6 mL O_2/kg/min; +18%) and males (+2.1 mL O_2/kg/min; +11%); these increases surpassed the

suggested clinically important change of 1.75 mL O_2/kg/min.[16,17] Additional health benefits observed following exercise training included improvements in several measures of AF-specific and general QoL, functional capacity, and CVD risk factors such as resting HR, waist circumference, anxiety and depression. Females reported greater AF frequency, duration and severity, had a higher resting HR and percent body fat, and lower body mass, fat-free mass and waist circumference than males. Both sexes were able to engage in 12 weeks of supervised exercise training, as shown by a high adherence and compliance with the program. Study 3 provided original data applicable to both sexes on the chronic effects of exercise training, and potential sex differences, yet the generalizability was limited given the small sample of females included, who were predominantly White, and the single-centre nature of the RCTs. We aimed to address these limitations in Study 4 by conducting a systematic review using a sex-specific lenses.

Study 4: Systematic review of the chronic effects of exercise training with a sex lenses in patients with atrial fibrillation

Since few studies have previously performed sex-based analyses, sex and gender guidelines recommend pooling sex-specific raw data of studies for performing meta-analyses.[18,19] The final study involved conducting a systematic review and meta-analysis pooling available sex-specific data from previous exercise studies in patients with AF, with the aim of comparing the chronic effects of exercise training on $\dot{V}O_{2peak}$, and additional physical and mental health outcomes, between females and males with AF (Chapter 6). Given its prognostic value, $\dot{V}O_{2peak}$ was the primary outcome.[9] Studies across all AF subtypes and implementing any type of exercise training for at least 4 weeks were considered eligible to increase the generalizability of findings. After searching 5 databases and contacting authors to obtain sex-specific data, 18 studies were included. Consistent with Study 3, our results revealed that following exercise training of 6 weeks to 1 year in duration, the change in $\dot{V}O_{2peak}$ did not

differ between sexes (mean difference [MD]= +0.22, 95% CI -1.13 to +1.57 mL O_2/kg/min). Smaller improvements in AF severity (MD=+1.00, 95% CI +0.13 to +1.87 points), general health perceptions (MD=-3.71, 95% CI -6.88 to -0.55 points) and systolic blood pressure (MD=+3.11, 95% CI +0.14 to +6.09 mmHg) were found in females than males. Less than 30% of participants in this review were females, despite females representing 47% of patients with AF.[20] The underrepresentation of females in clinical trials continues to hinder establishing clear conclusions in sex-specific research. Thus, enhancing the inclusion of females and other minority groups (e.g., non-white communities) in future exercise studies was identified as a major direction for future work. A visual abstract summarizing the four studies of this dissertation is presented in Figure 7.1.

Major limitations of the dissertation studies

Several overall limitations merit consideration. The Oxycon Mobile became available approximately halfway through the Opportunity trial, combined with unforeseen problems with this equipment, several participants were missing a follow-up $\dot{V}O_{2peak}$ value. $\dot{V}O_{2peak}$ remained the primary outcome as irrefutable evidence supports an inverse, proportional relationship between $\dot{V}O_{2peak}$ and the risk for CVD events and mortality.[9,21,22] I planned to incorporate sex and gender lenses in my dissertation, yet we did not collect enough gender-related data from inception in the RCTs, and barriers to scoring the Genesis-praxy in the Acute-AF study became apparent (e.g., the survey includes several modified scales for which scoring is not openly available for the public; only studies with a large sample size may be able to compute the gender score using principal component analysis).[23,24] Thus, only sex-based analyses were conducted. Most participants in the studies were Caucasian, limiting the applicability of our results. The generalizability to very frail patients with AF (~54% patients with AF are frail[25]) is also unknown. The use of the baseline cardiopulmonary exercise test for exercise prescription is a strength, as individuals with a lower baseline fitness level were

given a HIIT prescription adjusted to their needs using an objective measure of exercise intensity (peak power output). However, not all patients with AF may be able to perform an exercise test to exhaustion. Finally, studies 1 (Acute-AF trial) and 3 (RCTs) did not reach the *a priori* sample size, and the sex representation was unequal. Recruitment challenges due to the Covid-19 pandemic and barriers to the enrollment of females in clinical trials[15,26–29] may have contributed to not meeting these recruitment targets. Nonetheless, this work is a needed and critical step forward in improving our understanding of sex differences in the acute and chronic responses to exercise training in patients with AF.

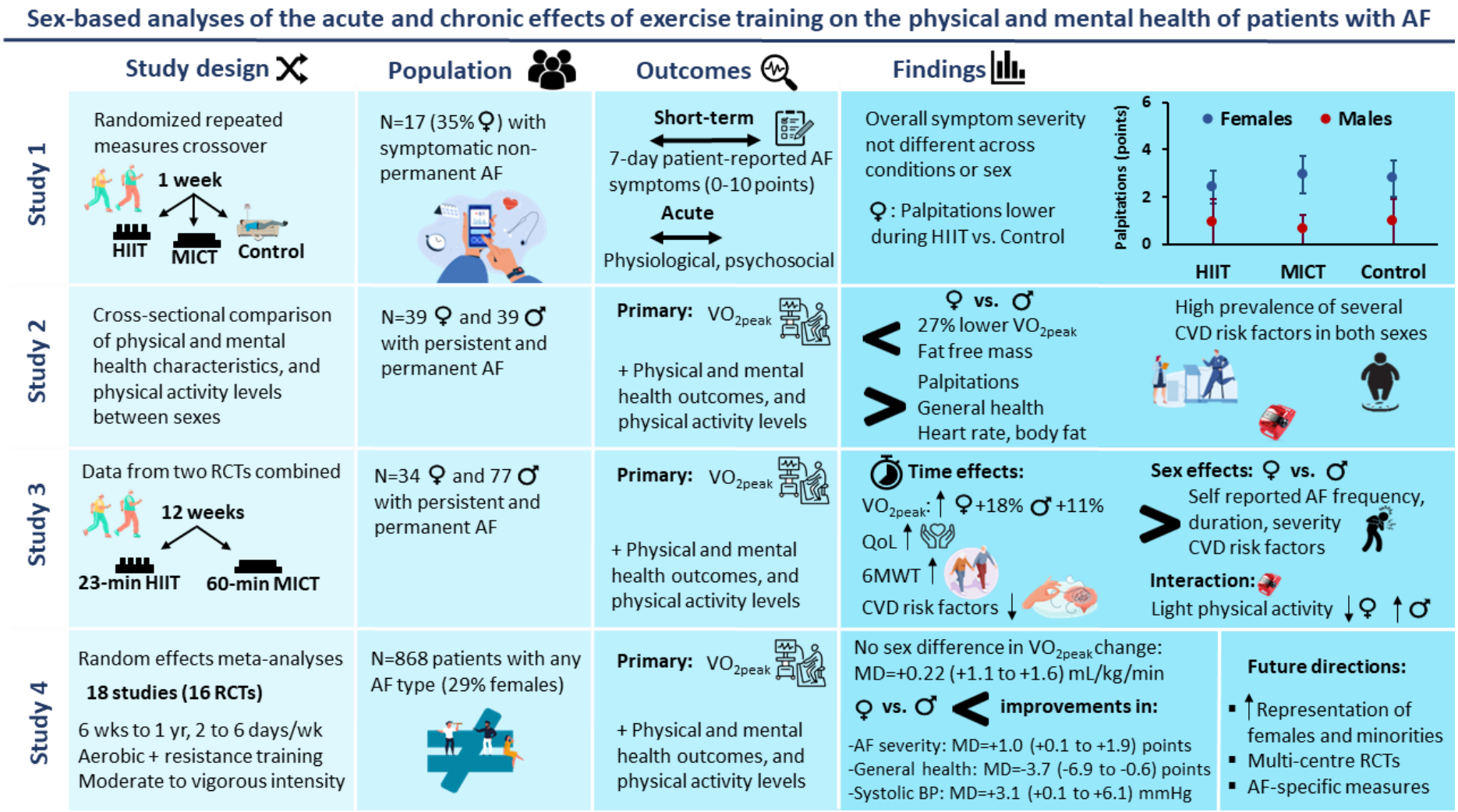


Figure 7.1. Visual abstract summarizing the four studies of this dissertation. 6MWT: Six-minute walk test; AF: Atrial fibrillation; BP: Blood pressure; CVD: Cardiovascular disease; HIIT: High-intensity interval training; MICT: Moderate- to vigorous-intensity continuous training; MD: Mean difference; QoL: Quality of life; RCT: Randomized controlled trial; $\dot{V}O_{2peak}$: peak aerobic power; yr: Year; wk: Week. (>): Higher than the other sex; (<): Lower than the other sex; (↑): Increased after exercise training; (↓): Decreased after exercise training; ♀: Females; ♂: Males.

7.2. Dissertation findings in the context of expanding literature and future directions

Since the beginning of this dissertation work four and a half years ago, advancements in the state of the evidence on the use of exercise training for the management of patients with AF and in sex-based research have been published. In this section, I discuss this evolution based on several published articles to inform how this dissertation fits within the current literature, potential implications for the care of patients with AF, and propose future research directions. This dissertation is timely as shown by the: (1) enhanced importance of exercise for the management of patients with AF;[30–32] and, (2) emerging clinical sex differences identified in the health of patients with AF.[5]

Enhanced importance of exercise training for the management of atrial fibrillation

The 2020 Canadian Cardiovascular Society (CCS)/ Canadian Heart Rhythm Society (CHRS) guidelines for AF management were the first to include specific exercise targets, recommending patients engage in at least 200 minutes per week of moderate-intensity aerobic exercise training, resistance training 2 to 3 days per week, and flexibility at least 2 days per week.[32] The CCS/CHRS are the only AF guidelines globally endorsing such specific targets, and the justification for them is unclear.[14,32,33] Whilst their inclusion in the guidelines has been commended, we have highlighted key gaps warranting further investigation.[14] For instance, the most effective exercise paradigms for improving patient AF symptoms and QoL remain misunderstood.[14] Interestingly, other researchers have proposed different targets of 60 to 120 minutes of moderate- to vigorous-intensity exercise per week based on evidence from recent prospective and retrospective exercise trials in patients with AF.[34] Including multi-disciplinary expertise in the task force responsible for the CCS/CHRS guidelines may address these inconsistencies.

The current debate is whether exercise-based cardiovascular rehabilitation (CR) should be part of routine care of patients with AF.[14,34] Participation in CR is a moderate-to-strong recommendation for the management of patients with a wide variety of CVD diagnoses and interventions (e.g., myocardial infarction, heart failure, peripheral artery disease, valve replacement), as it significantly decreases CVD morbidity and mortality and improves patients' QoL.[35–37] Yet, the role of CR in managing AF remains unclear.[34]

Study 1 revealed that AF symptoms may not be exacerbated in the short term with exercise training. Our descriptive physiological and psychosocial acute responses in patients with AF appeared similar to those seen in other CVD populations.[38–40] Four adverse events were noted during the study period. Given the older age of patients with AF, and the frequent co-morbidities and disabling nature of AF, we surmise that adverse events may be more frequent than in other, lower risk CVDs. In turn, exercise programs may need more flexibility to meet patient needs based on their current health status (e.g., lower the exercise volume when patient's health is compromised, offer supervised at-home exercise sessions to reduce transportation barriers to access the hospital, give patients clear guidance on the steps to take during AF episodes).

Data from Study 3 support that a 12-week exercise program leads to improvements in a few subscales of AF-specific and general QoL, functional capacity, and CVD risk factors. Previous trials in patients with AF have shown heterogeneous findings: following chronic exercise training, improvements in none,[41] one subscale,[42] and the physical and mental component summary scores[43–45] of the SF-36 have been reported. Engaging in combined aerobic and resistance training for 60 to 75 minutes, 3 days a week for 8 to 12 weeks led to clinically significant (≥5 points) improvements in several SF-36 subscales in patients with permanent AF.[45,46] Consistent with our findings, more compelling evidence (e.g., higher quality RCTs) supports improvements in $\dot{V}O_{2peak}$,[44,47–52] functional capacity[53–55] and resting

HR.[41,46,52,56] AF-specific QoL[48] and other CVD risk factors such as body composition have been rarely assessed,[57] and few reductions in anxiety and depression have been noted.[48,54]

Limitations in current evidence may be why current guidelines for the management of patients with AF do not endorse CR participation. For instance, when compared to other CVDs such as heart failure, there have been few trials enrolling patients with AF, most of which are relatively small, based on a single center, include few AF-specific measures, report heterogeneous findings, and several studies are not randomized trials.[14,34] Multi-centre trials are needed to provide high-quality, guideline-changing evidence that can positively impact the care of these patients, as many continue to report disabling symptoms and poor QoL with the traditional pharmacological and procedural treatment options.[4] In the next section, I discuss some of our findings with a sex lenses. It should be noted that the lack of sex-based analyses in exercise trials limits our ability to compare with other literature.

Emerging evidence on sex differences in patients with atrial fibrillation

More than 17.8 and 19.8 million females and males have an AF diagnosis worldwide, respectively.[20] Our sex-based analyses are a first step to ensure that the exercise recommendations are equitable for females and males with AF. There have been advancements in our understanding of sex differences in patients with AF, but progress has been slow,[5,14,58,59] and the quality of sex-based analyses poor with predominantly retrospective designs.[59] The sex differences identified in our cross-sectional comparisons (Study 2) agree with previous literature showcasing that females report palpitations[60–63] and have faster resting HRs.[62,64] Similar to healthy and CVD populations,[65] data from Studies 1 to 3 reveals that, in adults with AF, sex differences in $\dot{V}O_{2peak}$ are predominantly driven by females' smaller body size and mass, higher body fat and lower muscle mass than males.[65] Females' greater general health in Study 2 contrasts with findings from a previous systematic

review reporting consistently poorer QoL in females than males with AF.[66] The findings of our RCTs (Study 3) indicate that the improvements in physical and mental health following 12 weeks of exercise training did not differ by sex. However, females reported worse AF-specific QoL and had higher resting HRs and body fat; the latter have been associated with AF pathophysiology and recurrence.[67]

Our systematic review (Study 4) revealed that several health outcomes (i.e., AF severity, general health and blood pressure) may not improve as much in females than males with AF following chronic exercise training. Sub-analyses did not show whether a specific exercise paradigm or dose may be preferrable in each sex. Thus, females may need more targeted interventions to enhance improvements in health outcomes, but it remains unclear how to best meet their needs. CopenHeartRFA is the only CR trial in patients with AF where authors reported outcomes by sex, yet they did not conduct sex-based analyses.[47] Following CR, both sexes improved functional capacity, AF-specific QoL improved in females, and anxiety improved in males, when compared to non-exercise usual care.[47] Interestingly, our systematic review revealed significantly greater improvements in several health outcomes (i.e., $\dot{V}O_{2peak}$, general QoL, resting HR and blood pressure, and anxiety symptoms) in males following an exercise intervention when compared to non-exercise usual care. Yet, such significance was not found in females, likely due to the small sample of females. Providing more evidence on females and examining the influence of gender on the responses to exercise training is another research area needing future work.

Whilst our systematic review addressed the lack of sex-based analyses in prior trials, the fact that none of the previous exercise trials analyzed their results by sex, and that we were unable to obtain sex-specific data from more than 40 eligible studies calls into question whether the research community is conscious of and accountable for the consequences of such research practices. The historic male-bias in research studies has negatively impacted

the health of females for decades, as the foundations of clinical research and care may not serve females and males equitably.[15,68,69] The underrepresentation of females in this dissertation work aligns with research data in other CVD populations[15,26,58] and showcases that we need to change the status quo, as we have been designing clinical research studies in a way that does not meet the needs of females.[15] The enrolment of patients from diverse racial and ethnic backgrounds is even lower.[15,26] To revert the status quo, I reflect on the underrepresentation of females in AF and CVD trials, and how we can move forward.

There is a dire need to address the underrepresentation of females and other minority groups in CVD trials, and the lack of outcome reporting by sex

Our sex-based analyses represent a step forward in the inclusive advancement of the fields of exercise training and AF, yet barriers to enrolment of minority groups remain.[15,26] With the goal that future studies will implement more appropriate strategies to address such inequities, a brief reflection on the evolution of the importance of sex and gender considerations, and practical examples to enhance representativeness in future AF trials is provided.

Females have been historically excluded from clinical trials without appropriate justification.[15] For instance, in 1977 the Food and Drug Administration advised the exclusion of females of childbearing age from Phase I and Phase II drug trials. When the negative consequences of this negligence became apparent (e.g., birth of babies with limb deformities after taking the drug thalidomide during pregnancy), new policies emerged to address female underrepresentation in research studies.[70] In 1993, the National Institutes of Health (NIH) in the US mandated the inclusion of females in NIH-funded clinical trials.[71] It took another 20 years for the Canadian Institutes of Health Research (CIHR) to integrate mandatory questions regarding sex and gender considerations within grant applications.

Several approaches have been applied to support more inclusive trials, such as mandates from funding agencies, special issues in scientific journals, calls for action from renowned scientists and clinicians,[15,18,19,72] and the development of specialized centers of research excellence on sex differences (SCORE). Yet, females remain underrepresented relative to disease distribution across most disease populations, and the majority of researchers fail to report their data by sex and/or gender.[14,15,58] The statistics are even more concerning when it comes to patients from diverse racial and ethnic backgrounds, and transgender participants who are marginalized and have ongoing mistrust towards the research and healthcare systems following harmful practices inflicted in these populations (e.g., Tuskegee study).[15,73] Among 134 AF-related RCTs, only 13% reported enrollment of ethnic/racial minorities.[74] This is problematic as the use of sex, gender and race/ethnicity lens is critical to enhance the quality and applicability of health research.[68]

Since such policies at the organization-level have resulted in little progress, specific, practical strategies that can be implemented by individual scientists include:[15,73] (1) develop culturally adapted recruitment material and strategies (cultural competency training for staff may be needed); (2) create meaningful partnerships with community and patient advocacy groups (e.g., discuss barriers to research participation, which outcomes are most meaningful for patients); (3) design multi-centre trials with strategically selected sites (e.g., near where marginalized communities live); (4) remove unjustified eligibility criteria, including based on sex (e.g., pregnancy, lactation), age, co-morbidities or other demographic characteristics; (5) carefully design the consent process (e.g., involve next of kin in discussions); (6) minimize the research burden on participants (e.g., virtual follow-ups, compensation for transportation); and, (7) enhance diversity among trial leaders (e.g., provide research salary support and mentorship to train and retain females and researchers from diverse racial and ethnic backgrounds).[15] The latter suggestion may benefit AF research in particular. In support, male-

only trial leadership teams have been associated with a greater under-enrollment of females.[75] Only 13% of AF-specific RCTs published in top-tier journals between 2011 and 2021 were led by females,[58] revealing an area for improvement. Finally, strategies to enhance representation should be combined with *a priori* consideration of the most appropriate trial design (e.g., use demographic characteristics of interest such as sex as stratification criteria for randomization) and statistical plan (e.g., pre-specified sub-analyses, biostatistician involvement).[15,18,19,23] Knowledge mobilization of the Sex and Gender Equity in Research (SAGER) guidelines may also aid researchers in understating best practices for reporting sex and gender in research. Applying such recommendations in future exercise studies in patients with AF, and creating a research culture of respect and accountability, will lead to more generalizable evidence that serves females and males more equitably.

7.3. Conclusions

These four studies provide novel insights on the role of sex in the acute and chronic effects of exercise training on the physical and mental health of adults with AF. This dissertation showed that: (i) despite patient concerns of exercise-induced AF symptoms, exercise may not acutely worsen AF symptoms; (ii) several sex differences in the physical health profile and AF symptoms were observed, with a high prevalence of modifiable CVD risk factors in both sexes at baseline; (iii) our original data and systematic review showed that improvements in $\dot{V}O_{2peak}$ and several self-reported and objective health measures did not differ by sex following exercise training, yet, our meta-analyses revealed smaller improvements in patient AF severity, general health perceptions and systolic blood pressure in females than males following exercise training; and, (iv) future AF trials in patients with AF must improve the representation of females to establish clearer conclusions regarding sex-specific exercise research.

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