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Physical activity and the structure and function of the left side of the heart

Findings from a general adult and elderly population: The Tromsø Study

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Paper II

Heitmann KA, Løchen M-L, Hopstock LA, Stylidis M, Welde B, Schirmer H, & Morseth B. **Cross-sectional associations between accelerometry-measured physical activity, left atrial size, and indices of left ventricular diastolic dysfunction: The Tromsø Study.** *Prev Med Rep.* 2021;21:101290.

Paper III

Heitmann KA, Løchen M-L, Stylidis M, Hopstock LA, Schirmer H, & Morseth B. **Associations between physical activity, left atrial size and incident atrial fibrillation: the Tromsø Study 1994-2016.** *Open Heart.* 2022;9:e001823.

Abbreviations

AF: atrial fibrillation

ANCOVA: analysis of covariance

CPM: counts per minute

HR: hazard ratio

ICD: International Classification of Diseases

LA: left atrial

LADi: left atrial diameter index

LAVi: left atrial volume index

Light/Hard-PAQ: Light/Hard physical activity questionnaire

LDL: low-density lipoprotein

LV: left ventricular

LVMi: left ventricular mass index

MVPA: moderate-to vigorous physical activity

PA: physical activity

SGPALS: Saltin-Grimby Physical Activity Level Scale

Summary

Background: Current knowledge about the relationship between exercise and cardiac remodelling is mostly based on studies of athletes. Little is known about cardiac adaptations to moderate doses of exercise in the general adult and elderly population, and whether exercise-induced cardiac remodelling is a benign physiological adaption of exercise or part of a pathophysiological mechanism. Moreover, the association between physical activity (PA), cardiac remodelling and long-term risk of incident atrial fibrillation (AF) is complex and represents a knowledge gap, particularly in the general adult and elderly population.

Objective: The main objective of this thesis was to study the association between PA and the structure and function of the left side of the heart. Also, we wanted to explore if exercise-related left atrial (LA) remodelling was associated with adverse cardiac alterations and increased risk of incident AF.

Methods: In paper I, we applied a longitudinal design with repeated measures of self-reported PA and echocardiographic structural and functional data. In paper II, we applied a cross-sectional design to investigate the association between device-measured PA and LA size. In paper III, we applied a prospective design to investigate the association between self-reported PA, LA size, and risk of AF.

Results: The main findings of this thesis are that exercise-induced cardiac remodelling also occurs with moderate levels of habitual PA, and not only in endurance-trained athletes. Moreover, our results indicate that exercise-induced LA remodelling is a benign physiological adaptation to exercise, without being associated with reduced left ventricular (LV) diastolic function or increased risk of incident AF.

Conclusion: Higher levels of PA were associated with increased LA size in general, and increased LV size in females. However, no change in pump function or atrioventricular ratio at rest was observed with higher levels of PA. Moreover, moderate levels of habitual PA were associated with reduced risk of AF, and active individuals with LA enlargement did not have higher risk of AF than either active or inactive with normal LA size.

Sammendrag

Bakgrunn: Nåværende kunnskap om sammenhengen mellom trening og hjerteremodellering er for det meste basert på studier av idrettsutøvere. Lite er kjent om hjertetilpasninger til moderate doser trening i den generelle voksne- og eldre befolkningen, og om treningsindusert hjertemodellering er en normal fysiologisk tilpasning til trening, eller en del av en patofysiologisk mekanisme. Dessuten er sammenhengen mellom fysisk aktivitet (FA), hjerteremodellering, og langtidsrisiko for atrieflimmer (AF) kompleks og representerer et kunskapshull, spesielt i den generelle voksen og eldre befolkningen.

Hensikt: Hovedmålet med denne avhandlingen var å studere sammenhengen mellom FA og hjertets venstre sides struktur og funksjon. Vi ønsket også å undersøke om treningsrelatert remodellering av venstre atrium (VA) var assosiert med uønskede hjerteendringer og økt risiko for AF.

Metoder: I artikkel I brukte vi et longitudinelt design med gjentatte mål av selvrapportert FA og ekkokardiografiske strukturelle og funksjonelle data. I artikkel II brukte vi et tverrsnittsdesign for å undersøke sammenhengen mellom monitormålt FA og VA-størrelse. I artikkel III brukte vi et prospektivt design for å undersøke sammenhengen mellom selvrapportert FA, VA-størrelse og risiko for AF.

Resultater: Hovedfunnene i denne avhandlingen er at treningsindusert hjerteremodellering også forekommer ved moderate nivåer alminnelig FA, og ikke bare hos utholdehetsutøvere. Dessuten indikerer resultatene våre at treningsindusert VA-remodellering er en normal fysiologisk tilpasning til trening, uten å være assosiert med redusert venstre ventrikkel (VV) diastolisk funksjon eller økt risiko for insidens av AF.

Konklusjon: Høyere nivåer FA var assosiert med økt VA-størrelse generelt, og økt VV-størrelse hos kvinner. Imidlertid ble ingen endring i pumpefunksjon aller atrioventrikulært forhold i hvile observert ved høyere nivåer FA. Moderate nivåer FA var assosiert med redusert risiko for AF, og aktive individer med VA-forstørrelse hadde ikke høyere risiko for AF enn hverken aktive- eller inaktive med normal VA-størrelse.

1 Introduction

As early as in the late 1890s, cardiac enlargement was recognised in cross-country skiers by Salomon Henschen by auscultation and percussion [1], and later the same year by Eugene Darling in university rowers [2]. The initial findings of Henschen and Darling were later confirmed in the early 1960s by chest radiography showing global cardiac enlargement in athletes [3,4], and by electrocardiography in the mid-1960s [5].

1.1 Exercise-induced cardiac remodelling

Since the initial reports by Henschen and Darling, the development of advanced echocardiographic techniques and cardiac magnetic resonance imaging has increased our understanding of exercise-induced cardiac remodelling. It is now well documented that intensive and chronic exercise leads to structural, functional, and electrical adaptations in the heart, often referred to as exercise-induced cardiac remodelling or "athlete's heart" [6]. Exercise-induced cardiac remodelling is generally considered a benign physiological adaption to the increased hemodynamic load of exercise, and also includes left atrial (LA) and left ventricular (LV) chamber enlargement, and increased LV wall thickness [6,7].

It is well known that a large stroke volume and cardiac output are essential for high cardiorespiratory fitness and endurance performance [8]. The main cardiac adaptations to systematic endurance training are enlarged chambers and the accompanying capability to generate a large stroke volume [9], and the extent of cardiac enlargement is proportional to the level of cardiorespiratory fitness [10,11].

The focus of this thesis in to explore associations between physical activity (PA) and the structure and function of the left side of the heart.

1.1.1 Structural remodelling of the left side of the heart

Numerous meta-analyses have concluded that LA and LV chamber sizes generally are larger in endurance-trained athletes in comparison with non-athletes or sedentary controls [12-15]. In a recent meta-analysis including over 7000 elite athletes, Iskandar and colleagues [14] reported that athletes had 30% greater LA size compared with sedentary controls. Furthermore, among 1800 Italian elite-athletes, LA size exceeded upper normal limits (LA enlargement) in 20% of the athletes [16]. For the left ventricle, athletes typically have 10–20% larger LV wall thickness, and 10–15% LV cavity sizes compared with individuals of similar age and size [6]. In a study of

1300 Caucasian Italian Olympic athletes, LV chamber size exceeded the upper normal limits in 45% of the athletes, and 14% of these athletes had substantially enlarged LV size [17].

The relationship between endurance training and structural remodelling has also been demonstrated in experimental trials. In a recent meta-analysis, the authors concluded that LV volume and LV mass increased with endurance exercise in untrained males and females [18]. Likewise, one year of intensive endurance training increased LV volume and mass in young sedentary males and females [19]. Interestingly, Opondo and colleagues [20] demonstrated that LA and LV volume increased after ten months of high-intensity endurance training in middle-aged sedentary males and females. However, LA and LV volumes were considerably smaller when compared with a control group of age-matched endurance athletes with a long history of endurance training [20].

1.1.2 Functional remodelling of the left side of the heart

Despite LA and LV enlargement, several studies have observed that LV diastolic function is preserved [21-23], or even supranormal in athletes compared with healthy controls [24]. Furthermore, normal LV systolic function is also observed in athletes with cardiac chamber enlargement [17,23].

In a meta-analysis of ventricular structure and function, preserved LV systolic function in athletes was confirmed in males and females, both at rest and during exercise [13]. Moreover, LV systolic function did not differ between athletes and matched control subjects [13]. Similar results were reported in a recent meta-analysis of endurance training trials, where the authors concluded that LV systolic function slightly increased in males, but was unaltered in females [18].

Also, in the general adult and elderly population, LA enlargement was not associated with reduced LV diastolic function [25]. In accordance, indices of LV diastolic dysfunction were associated with LA enlargement in non-athletes, but not in athletes [26]. Moreover, a low cardiorespiratory fitness level was associated with LV diastolic dysfunction, whereas a higher level of fitness was associated with lower prevalence of LV diastolic dysfunction [27].

1.1.3 Mechanisms explaining exercise-induced cardiac remodelling

The physiological mechanisms causing exercise-induced chamber remodelling are related to the haemodynamic overload on the myocardial walls due to increased stroke volume and

cardiac output during exercise [28-30]. During exercise, the myocardial walls acutely stretch in response to the increased pressure and volume overload, which initiates release of multiple growth factors from multiple cardiac cells ultimately leading to cardiac enlargement [29,30]. As the hemodynamic stretch-stimulus for exercise-induced cardiac remodelling only is present during exercise, the magnitude of cardiac remodelling likely depends on cumulative time spent exercising [28,29].

1.2 Exercise-induced cardiac remodelling may mimic pathological remodelling

Exercise-induced chamber enlargement of the left atria and ventricle may overlap and mimic structural heart diseases, such as hypertrophic, or dilated cardiomyopathies [6,28,30,31], and therefore represent a diagnostic challenge for clinicians [14,16,31].

In a study of 1800 highly trained athletes, 2% of these athletes had LA enlargement that overlapped atrial dilation observed in patients with structural heart disease [16]. Furthermore, in a study of 1300 Olympic athletes, 14% of these athletes had substantially enlarged LV size, similar to LV dilation seen in patients with dilated cardiomyopathy [17].

Moreover, LA enlargement is one of the main criteria for the determination of LV diastolic dysfunction [32] and heart failure with preserved ejection fraction [33]. Also, LA enlargement is generally an independent risk factor for incident atrial fibrillation (AF) [30,34-37].

1.2.1 Difference between exercise-induced cardiac remodelling and pathologically remodelling

In athletes with LV enlargement, symmetrical biventricular enlargement, LV systolic function, or peak cardiorespiratory fitness may help distinguish between physiology and cardiomyopathy [6]. Moreover, LV systolic function is preserved or even supranormal in athletes, whereas LV systolic function is reduced in patients [31]. Furthermore, LV diastolic function is also preserved in athletes with LV enlargement [17,31], but reduced in patients with cardiomyopathy [31].

In athletes with LA enlargement, it is observed that LA function [38,39] and LV diastolic function [21,23] are preserved. Furthermore, despite structural similarities between exercise-induced LA enlargement and pathological LA enlargement, LA reservoir function may differentiate between physiological and pathological hearts [28]. Left atrial reservoir function

has been reported superior to volumetric measurements of LA size at revealing participants with AF [40], and has been reported to be an independent predictor of hypertrophic cardiomyopathy [41]. Also, balanced atrioventricular remodelling may help distinguish between physiology and cardiomyopathy [23,28].

Gabrielli and colleagues [41] compared cardiac function between athletes, patients with hypertrophic cardiomyopathy, and controls matched for age, sex and body surface area. Both athletes and patients had LV hypertrophy and LA enlargement with similar LV and LA sizes. However, patients had lower LV systolic and diastolic function than athletes, whereas athletes and controls had similar LV systolic and diastolic function [41]. Moreover, despite LA enlargement, athletes had similar LA emptying fraction and reservoir function as controls, whereas patients had reduced LA emptying fraction and reservoir function [41].

1.3 Left ventricular diastolic dysfunction

The ventricle has two alternating functions, systolic ejection and diastolic filling [42]. LV diastolic dysfunction is defined as the inability to fill the left ventricle sufficiently at acceptable low pressures [43], and is an independent predictor of all-cause mortality in the general population [44]. Moreover, heart failure is generally caused by LV myocardial dysfunction (systolic, diastolic or both) [33], and the prevalence of heart failure increases with increasing age, affecting over 10% of adults >70 years [33]. Furthermore, lifetime risk of heart failure at age 55 is about one in three [45]. In patients with heart failure, approximately 50% have reduced ejection fraction, whereas 50% have preserved or mid-range ejection fraction [33].

LV diastolic dysfunction is assumed to be the underlying pathophysiological cause in patients with heart failure with preserved ejection fraction [45]. In addition, LV diastolic dysfunction is potentially the underlying cause in patients with heart failure with mid-range ejection fraction, and most patients with heart failure with reduced ejection fraction also have LV diastolic dysfunction [45].

1.3.1 Pathophysiology of left ventricular diastolic dysfunction

The fundamental pathophysiological mechanisms for LV diastolic dysfunction are impaired LV relaxation, increased LV stiffness, and loss of LV restoring forces (early diastolic suction) [32,46]. Consequently, LA pressure increases as a compensatory mechanism to preserve cardiac output when these mechanisms deteriorate [46].

Delayed LV myocardial relaxation in the early diastole is caused by reduced rate of calcium re-uptake from the cytosol and increases LV stiffness in early diastole [46]. Moreover, increased afterload or late systolic load will delay myocardial relaxation [42]. Furthermore, delayed relaxation leads to loss of LV restoring forces, which decreases passive filling of the left ventricle due to diastolic suction in the early diastole [46]. Moreover, restoring forces also reflect LV systolic function, as the left ventricle recoils back to its original shape when LV compression is released [46]. As a consequence of decreased passive filling in early diastole, LA pressure increases due to increased reliance on active filling in late diastole [46]. LV passive stiffness is dependent on elastic properties from the chamber, pericardium, and lungs [46], and increased stiffness of the myocardium is mainly due to changes in collagen and titin homeostasis [47].

During LV diastole, the left atrium is directly exposed to LV pressure via the open mitral valve [48]. Therefore, maximal LA volume normally reflects increased LV filling pressure over time, providing prognostic information about the severity and chronicity of LV diastolic dysfunction [32]. With worsening LV diastolic function, the LA pressure increases as a compensatory mechanism to preserve sufficient filling of the left ventricle, ultimately resulting in LA enlargement [46,48].

1.3.2 Risk factors for left ventricular diastolic dysfunction and heart failure

Modifiable risk factors for the development of heart failure include among other things sedentary behaviour, cigarette smoking, obesity, excessive alcohol intake, hypertension, dyslipidaemia, and diabetes [33]. Furthermore, structural heart disease and abnormal cardiac function are pathological mechanisms which ultimately may lead to heart failure [33]. Heart failure and AF often coexist through similar pathological alterations in the heart [33]. Moreover, as the risk factors often coexist [49,50], heart failure and AF may therefore trigger or worsen each other [50].

1.4 Atrial fibrillation

Atrial fibrillation is a supraventricular arrhythmia consisting of uncoordinated atrial electrical activation with subsequent ineffective atrial contractions [50]. Globally, AF is the most common arrhythmia, and is associated with mortality and morbidity, such as heart failure and stroke [50]. The prevalence of AF includes 43.6 million individuals worldwide [50], and the lifetime risk for

incident AF in individuals with European ancestry >55 years is one in three [50]. In Norway, cumulative prevalence of AF from 1994 to 2014 was 2.1% (n=6778) in the age group 55–59 years, and increased to 19.3% (n=20418) in the age group 80–84 years [51]. Globally, a 2.3-fold increase in AF is expected in the coming decades [50], mainly due to increased longevity in the general population and intensifying search for undiagnosed AF [50]. However, in addition to age, AF lifetime risk also depends on risk factors and comorbidities [50], suggesting that preventive strategies for risk factor control could reduce incident AF.

1.4.1 Pathophysiology of atrial fibrillation

The pathophysiology of AF involves a complex interplay of arrhythmogenic substrate development, triggers, and modulating factors, which result in AF occurrence [50], these factors are often referred to as the concept of Coumel's triangle of arrhythmogenesis [52,53]. The arrhythmogenic substrate usually consists of atrial structural, architectural, functional, and electrophysiological alterations, which promote the onset and continuation of the arrhythmia [54-56]. The trigger is usually a premature ectopic beat arising from the pulmonary veins ostia [57], but may also originate by presence of other synchronised tachyarrhythmias [54]. The modulating factors usually imply the sympathetic and vagal tone, and electrical remodelling [54,57].

Furthermore, the concept of atrial cardiomyopathy is considered an extension of the Coumel's triangle, and is suggested as a primary driver for AF [58]. Atrial cardiomyopathy affects all cellular parts of the atria, and manifests in three main ways (electrical, functional, and structural alterations) [58]. Electrical alterations include ion-channel remodelling and the corresponding development of low-voltage areas, causing progression of AF burden [58]. Functional alterations include increased LA size, reduced contractile function, and deteriorated conduit- and reservoir function [58]. Structural alterations include cardiomyocyte hypertrophy, atrial fibrosis, fatty infiltration, and LA dilation [58].

Several aetiological factors (e.g., hypertension, diabetes, heart failure, coronary artery disease, obesity, and genetic predisposition) causes atrial cardiomyopathy, consequently leading the atria to develop or maintain AF [50].

1.4.2 Risk factors for atrial fibrillation

Increasing age is the most prominent risk factor for incident AF [56,59], but other established AF risk factors include among other things male sex, hypertension, diabetes, obesity, heart

failure, and physical inactivity [50]. This is supported by data from the Atherosclerosis Risk in Communities Study, which estimated that the highest population-attributable fraction for AF was hypertension, body mass index, smoking, cardiac disease, and diabetes [60]. Moreover, the authors estimated that hypertension explained 21.6% of all AF cases, and that body mass index ≥30 kg/m^2 explained 17.9% of all AF cases [60]. Similarly, in a European population, Morseth and colleagues demonstrated that 20% of all AF cases in participants ≥60 years were attributed to hypertension, and that 15%–19% of all AF cases in participants between 50–70 years were attributed to body mass index >30 kg/m^2 [61]. An overview of risk factors for incident AF is presented in Table 1.

Moreover, LA enlargement is generally accepted as an independent risk factor for incident AF [30,34-37]. In the original Framingham study, increasing LA size was the strongest independent predictor of AF [30], and it has been estimated that for every 5 mm increase in LA diameter, risk of AF increases with 48% [36].

Table 1. Overview of risk factors for atrial fibrillation

Demographic and lifestyle-related factors	**Health and other risk factors**
Age [49,62-64]	Hypertension [49,60,62-64]
Male sex [49,62,63]	Systolic blood pressure [49,62-64]
Caucasian ethnicity [49,62,63]	Diastolic blood pressure [62,64]
Lower socioeconomic status [49]	Total cholesterol [49,64]
Smoking/tobacco use [49,60,62,64]	LDL-cholesterol [49,62]
Alcohol intake [64,65]	Triglycerides [49]
Physical inactivity [49]	Diabetes [49,60,62,64]
Vigorous exercise or endurance sport [66,67]	Renal dysfunction [49,68]
	Obesity/high body mass index [49,60,62-64]
Cardiovascular conditions/diseases	Height [49,62,64]
Heart failure [60,62,63]	Sleep apnoea [69,70]
Valvular disease [63,71]	Chronic obstructive pulmonary disease [72]
Coronary heart disease [60,62]	
Congenital heart disease [73]	**Inflammation**
Left atrial enlargement [62,74]	C-reactive protein [49,64]
Left ventricular hypertrophy [62]	Fibrinogen [49,64]
	Thyroid dysfunction [49]
Subclinical atherosclerosis	Autoimmunity [49]
Carotid IMT and carotid plaque [75]	Other biomarkers [64]
Coronary artery calcification [76]	
	Disorders of heart rhythm
Genetic factors	PR interval prolongation [62,63]
Family history of AF [77]	Sick sinus syndrome [78]
Genetics [79,80]	Wolff-Parkinson White [81]

IMT, intima-media thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Based on 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation [50].

1.5 Preventing left ventricular diastolic dysfunction and atrial fibrillation: Physical activity

Identification and management of comorbidities, cardiometabolic risk factors, and risk factors caused by lifestyle-related factors are recommended as a central part in primary prevention of AF [50]. Therefore, lifestyle interventions are recommended to manage and modify modifiable risk factors (e.g., obesity, hypertension, diabetes, and physical inactivity) and cardiac

pathology to prevent stroke and reduce risk for incident AF, as well as AF burden and progression [50].

Worldwide, PA is recommended for the promotion of health and prevention of diseases [82], and several meta-analyses has documented that moderate doses of regular PA reduces the risk of incident AF [83-86]. The beneficial effects of PA may be explained by improvements in modifiable risk factors [85,87] and by improved cardiorespiratory fitness [88].

Furthermore, studies have reported that athletes have normal LV diastolic and systolic function [22,23], or even supranormal LV diastolic function [24,89], and that active adults from the general population had favourable indices of LV diastolic and systolic function compared with less active individuals [90]. Moreover, a recent meta-analysis concluded that there was an inverse dose-response relationship between PA and risk of heart failure [91]. The protective effect of PA was likely explained by modification of risk factors, but also due to favourable changes in cardiac structure and function [91].

1.6 Exercise-related atrial fibrillation

In contrast to the cardioprotective effects of moderate PA, high levels of vigorous PA and regular endurance exercise may weaken the benefits of moderate PA, or even increase risk of AF [88,92], and a U-shaped relationship between exercise and risk of AF has been suggested [85,93-95]. A meta-analysis predominantly of male athletes estimated that elite athletes had a five-fold risk of AF compared with sedentary non-athletes [66]. Furthermore, in a large study of 53000 cross-country skiers (90% males), the authors reported that the risk of AF was related to the number of races completed and faster finish times (a proxy for the participants' lifetime exposure to physical exercise) [96]. Similarly, Mont and colleagues [34] reported that higher levels of accumulated lifetime exposure to exercise increased the risk of AF compared with age and sex-matched controls. In daily practice, exercise-related AF is generally diagnosed in young or middle-aged male athletes with a history of intense endurance sport practice [55,97]. Typically, these males are free from known diseases which may cause cardiac tissue damage or heart disease, but normally prove signs of exercise-induced cardiac remodelling [55]. Additionally, these males are usually normal weight, non-smokers, non-diabetic, and normotensive [55].

Several studies have tried to quantify the exercise thresholds for the onset of increased AF risk: Elosua and colleagues [98] estimated that >1500 hours of lifetime sports practice increased

the risk of AF in males. Similarly, Calvo and colleagues estimated that ≥2000 hours of cumulative high-intensity endurance training increased the risk of AF, whereas <2000 hours was associated with reduced AF risk [95]. Finally, in a prospective study including 44000 males, >5 hours/week of intensive exercise at the age of 30 increases the risk of AF [99].

1.6.1 Mechanisms explaining exercise-related atrial fibrillation

The exact causative mechanisms of increased AF risk in athletes, or with vigorous endurance exercise, are not fully understood, but several possible mechanisms may facilitate AF in athletes [87,97,100]. The factors constituting the Coumel's triangle of arrhythmogenesis (arrhythmogenic substrate, triggers, and modulating factors) may potentially be developed as a result of cardiac remodelling as an adaptation to endurance training and/or sports practice [54]. Exercise-induced atrial structural and functional alterations may induce and augment AF [54,55], and provoke premature atrial ectopic beats [57]. Moreover, exercise may induce alterations in sympathetic and vagal tone, electrical remodelling, and resting bradycardia [34,57,87,101], modulating factors that may reduce atrial refractory period and facilitate re-entry [30,97,102].

1.6.2 The left atrial substrate

As part of the Coumel's triangle, suggested mechanisms explaining the exercise-related AF risk include alterations of the left atria (enlargement, inflammation, and fibrosis) [55,97], which potentially constitute the arrhythmogenic substrate and may provoke triggers [55,97]. As a consequence of the hemodynamic overload during strenuous endurance exercise, atrial stretch may potentially release similar arrhythmogenic factors as in pathological conditions, and thereby trigger pathological remodelling and increase the risk of AF [30,97]. During strenuous endurance exercise, atrial stretch may potentially cause cumulative microstructural damage to the myocardium, and it has been hypothesised that such damage might develop after incomplete recovery between exercise sessions [97]. Therefore, repetitive- and cumulative stretch-induced stimuli of exercise training may potentially inflict cumulative microstructural damage, and therefore explain the increased risk of AF seen with large quantities of exercise [34,87,95].

However, the hypothesis that structural changes in the atria may cause AF are borrowed from pathophysiological models [103], and convincing data linking exercise-induced LA enlargement to AF are lacking and largely speculative [55,97,102]. Furthermore, in a study of 1800 competitive athletes, LA enlargement was frequently observed, whereas the prevalence of AF was low

(<1%) [16]. Moreover, exercise-induced LA fibrosis has only been hypothesized, but not documented in humans, despite exercise-induced LA enlargement [54,97,102]. In addition, D'Ascenzi and colleagues [104] reported that LA myocardial stiffness (a proxy for fibrosis) was normal or even lowered in the atria of female athletes compared with sedentary individuals. Moreover, despite larger LA size, athletes had lower LA myocardial stiffness compared with controls [103]. Noteworthy, it has been documented that acute strenuous endurance training may induce a short-term transient increase in circulating levels of proinflammatory biomarkers [105], and excessive endurance training or overtraining may potentially lead to chronic inflammation-related AF [106]. In contrast, regular PA seems to have a systemic anti-inflammatory effect, which may protect against oxidative stress and inflammation [97,105].

1.7 Rationale for the thesis

Current knowledge about the relationship between exercise and cardiac remodelling is mostly based on studies of athletes, mainly using a cross-sectional design. Little is known about cardiac adaptations to moderate doses of exercise in the general adult and elderly population [107,108], and studies exploring how the lower part of the exercise-spectrum associates with cardiac remodelling are therefore needed. Moreover, longitudinal and device-based studies are necessary for a more objective and nuanced understanding of how PA relates to cardiac remodelling.

Furthermore, cardiac remodelling is generally associated with pathophysiologies such as heart failure and AF. However, the association between PA, cardiac structure and function, and adverse effects needs further elaboration, to elucidate if exercise-induced cardiac remodelling is a benign physiological adaption of exercise, or part of a pathophysiological mechanism. The association between PA, cardiac remodelling and long-term risk of incident AF is complex and represents a knowledge gap, particularly in the general population.

2 Aims of the thesis

The main objective of this thesis was to study the association between PA and the structure and function of the left side of the heart. We aimed to complement current knowledge about cardiac adaptations to PA in the general adult and elderly population and, moreover, explore if exercise-related LA remodelling was associated with adverse cardiac alterations and increased risk of incident AF. We hypothesized that PA led to cardiac remodelling not associated with LV diastolic dysfunction.

The specific aims were:

1. To explore longitudinal associations between self-reported leisure-time PA and change in structure and function of the left side of the heart in a general adult and elderly population (Paper I).
2. To explore cross-sectional associations between accelerometry-measured PA and LA size in a general adult and elderly population. We also aimed to explore if LA enlargement was adversely associated with indices of LV diastolic dysfunction when accounting for PA (Paper II).
3. To explore prospective associations between self-reported leisure-time PA, LA size and incident risk of AF in a general adult and elderly population. Also, we aimed to explore if PA attenuated the increased risk of AF generally seen with LA enlargement (Paper III).

3 Materials and methods

This chapter offers a structured summary and overview of the materials and methods presented in the three original papers constituting this thesis [109-111].

3.1 The Tromsø Study

The Tromsø Study was initiated in 1974 and is an ongoing single-centre population-based cohort study with seven health surveys (referred to as Tromsø1–7) of the population of the Tromsø municipality, Norway [112]. All surveys include a visit with basic examinations of the total study sample, whereas Tromsø4–7 also includes a second visit with extended examinations (e.g., echocardiography) of the participants which was conducted two to four weeks after the first visit. The papers in this thesis are based on data from Tromsø4 (paper III), Tromsø6 (paper I), and Tromsø7 (paper I and II).

3.1.1 Tromsø4

In Tromsø4 (1994–95), all inhabitants ≥25 years were invited to the basic examinations (n=37558), with 27158 males and females attending the first visit (77% attendance). Of these, all males aged 55–74 years, all females aged 50–74 years, and 5–8% random samples of the other age groups aged 25–85 years were invited to the second visit. Of these, a total of 7965 participants (76% of the 10542 invited subjects) attended the second visit. These participants were alternately allocated by computer to one of two lines of examination when attending the first visit, and 3287 participants in one of the lines were examined by echocardiography.

3.1.2 Tromsø6

In Tromsø6 (2007–08) [113], all inhabitants aged 40–42 and 60–87 (n=12578), a 10% random sample of individuals aged 30–39 (n=1056), a 40% random sample of individuals aged 43–59 (n=5787), and participants from the second visit in Tromsø4, not included already (n=341), were invited to the basic examination (n=19762). Of these, a total of 12981 males and females aged 30–87 years participated in the first visit (66% attendance). Of these, 7307 participants (64% of the originally pre-marked sample, and 92% of those invited to the second visit) attended. Individuals who were invited to the second visit were those who fulfilled one of the following criteria: 1) All individuals aged 50–62 and 75–84 years (n=7657), 2) 20% random sample of males and females who were eligible for the first visit and were aged 63–74, if not

already included (n=942), or 3) participants, if not already included, who attended the second visit in Tromsø4 and were aged <75 years (n=2885).

3.1.3 Tromsø7

In Tromsø7 (2015–16) [114], all inhabitants aged ≥40 years (n=32591) were invited to the basic examination. A sub-sample (n=13028) was pre-marked for invitation to participate in the second visit conducted approximately two weeks later. This was a) a randomized sample (n=9925), and b) Tromsø6 (2007–2008) participants who attended body composition, echocardiography, and eye examinations (n=3103). A total of 21083 males and females aged 40–99 years attended the first visit (65% attendance). A total of 8346 attended the second visit (64% of the originally pre-marked sample and 90% of those who attended the first visit). Of these, 6300 participants have data on accelerometry-measured PA, and 2340 have data on echocardiography.

3.2 The study population

Paper I is a longitudinal study based on data from Tromsø6 and Tromsø7, with repeated measurements of PA and echocardiographic structural and functional data. In total, 623 participants provided valid data on self-reported PA in combination with valid echocardiography data from Tromsø6 and Tromsø7. We excluded participants with valvular heart disease at baseline (n=21). Furthermore, 8 participants were excluded due to missing data on the covariate hypertension. Finally, our analytical sample consisted of 594 participants free from valvular heart disease, and with valid data on PA, echocardiography, and covariates at baseline (Figure 1).

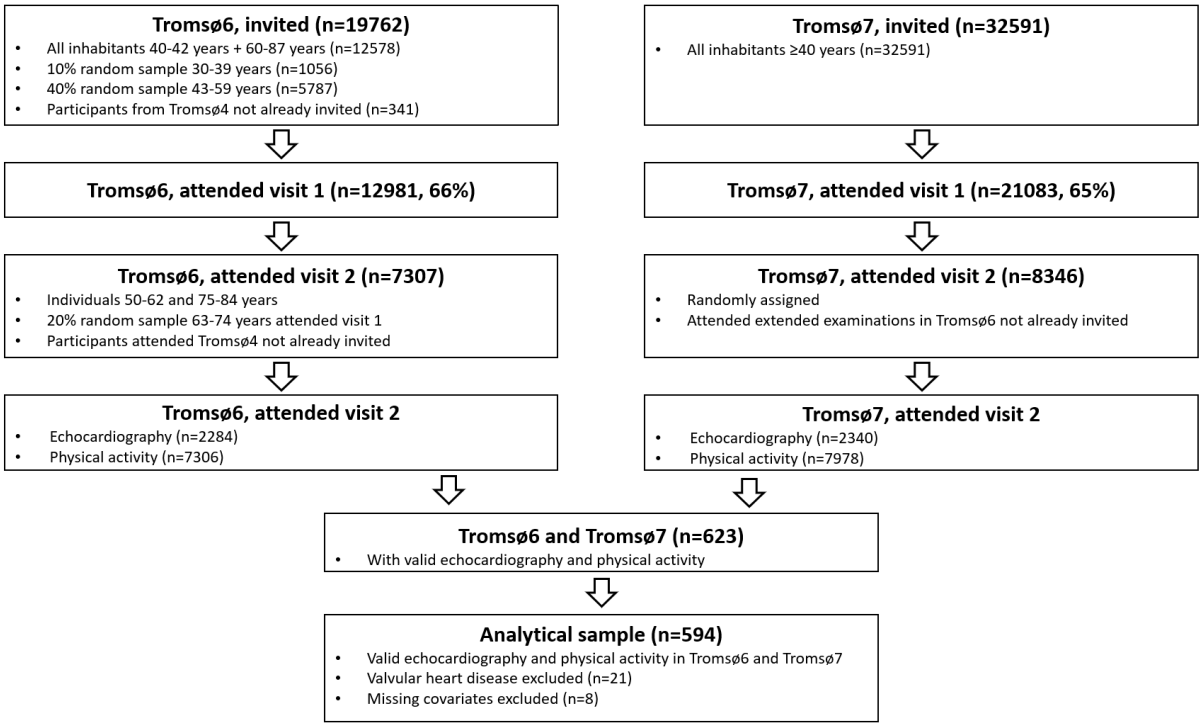

Figure 1. Flowchart over inclusion of participants in paper I: The Tromsø Study 2007–2016.

Paper II is a cross-sectional study based on data from Tromsø7. In total, 1651 participants had valid data on both accelerometry-measured PA and echocardiography, and 1573 had valid data on accelerometry-measured PA and echocardiography in addition to all covariates (Figure 2).

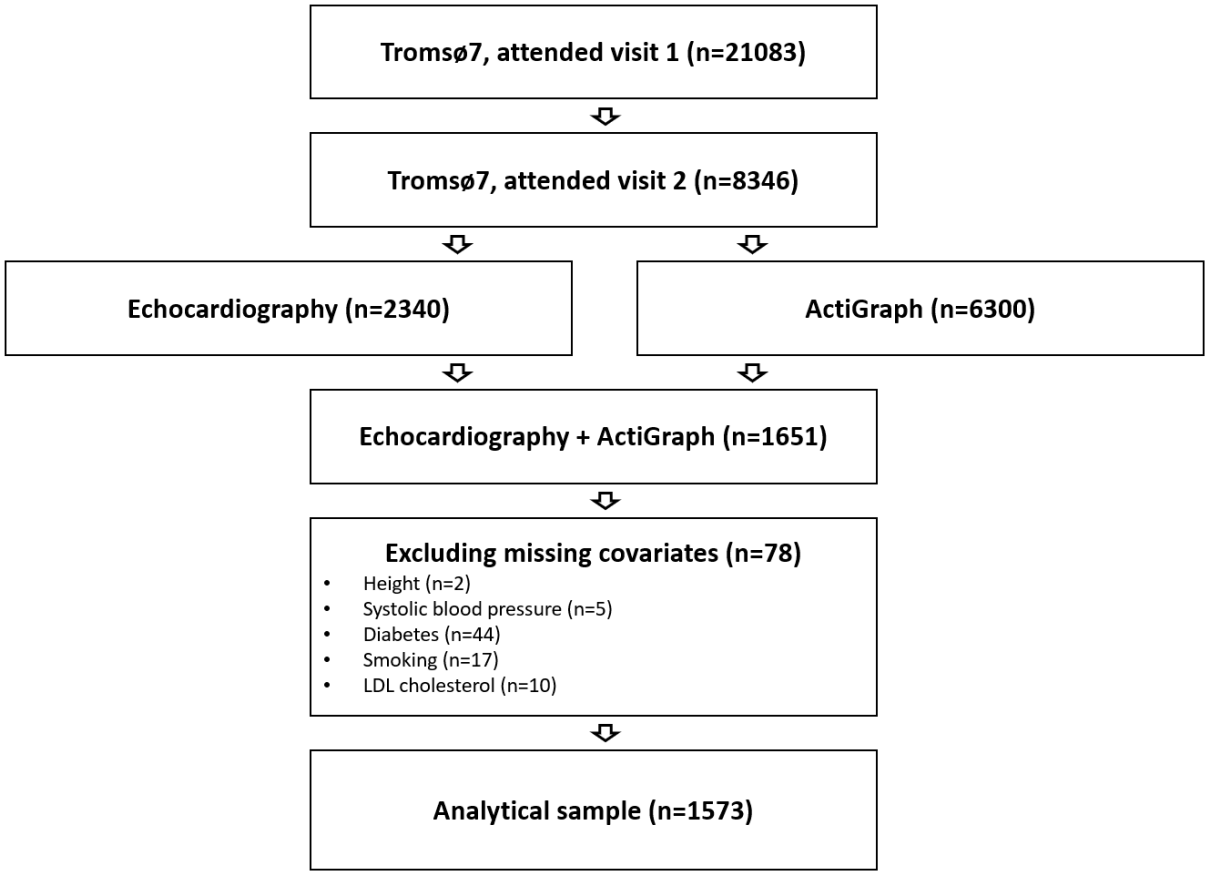

Figure 2. Flowchart over inclusion of participants in paper II: The Tromsø Study 2015–2016. LDL, low-density lipoprotein.

Paper III is a prospective study based on data from Tromsø4, where the participants were followed up for incident AF to the end of follow-up on 31 December 2016. In total, 2714 participants provided valid data on PA in combination with valid echocardiography data and status of known cardiac pathologies at baseline. We excluded participants with previous or present documented AF (n=45), valvular heart disease (n=27), LV ejection fraction <40% (n=13), previous myocardial infarction (n=129), and LA below normal reference range (n=16) at baseline. Furthermore, one participant was excluded due to missing data on a covariate (systolic blood pressure), and four participants were excluded as they migrated before date of baseline. Finally, our analytical sample consisted of 2479 participants free from known cardiac pathology, and with valid data on PA, AF, echocardiography, and covariates at baseline (Figure 3).

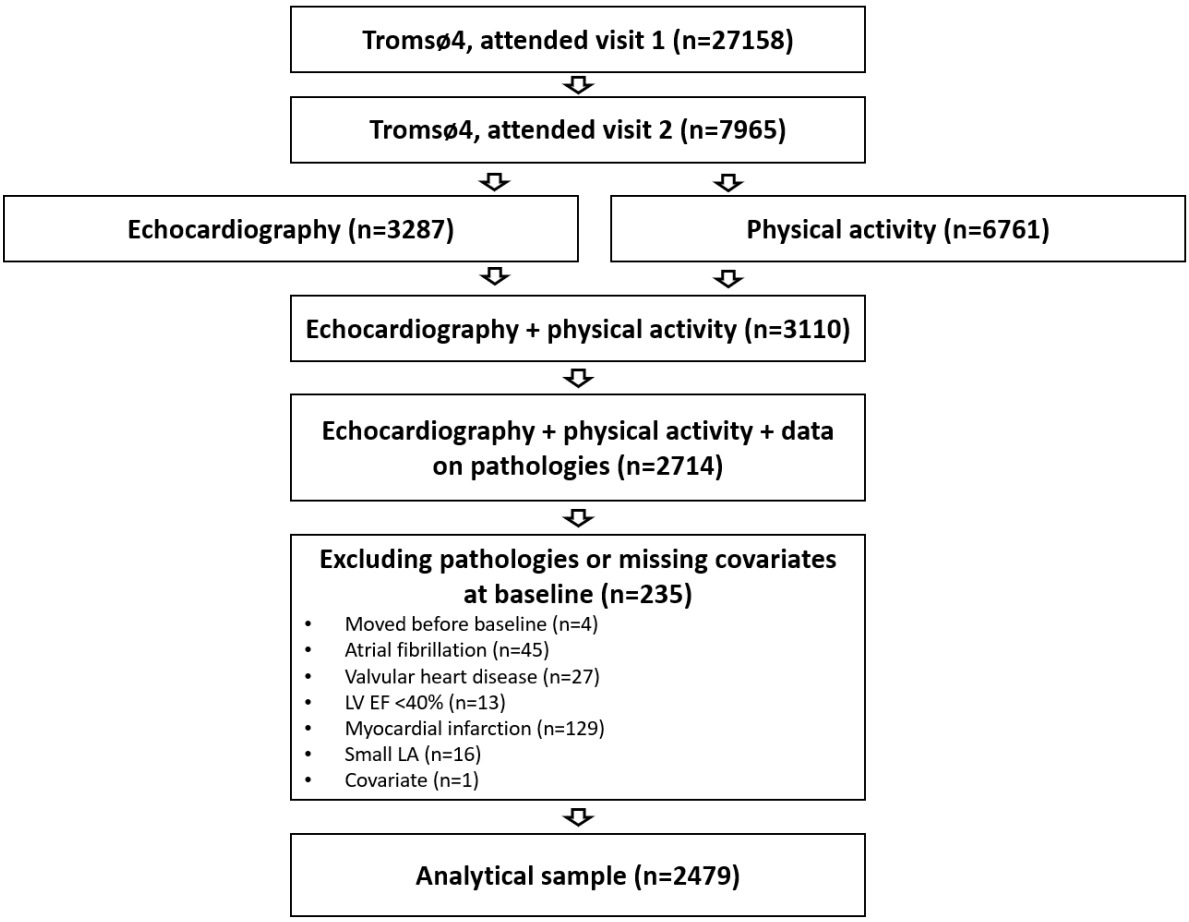

Figure 3. Flowchart over inclusion of participants in paper III: The Tromsø Study 1994–2016. LV, left ventricular; EF, ejection fraction; LA, left atrial.

3.3 Ethics

The Tromsø Study complies with the Declaration of Helsinki. The Tromsø Study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics. In Tromsø4–7, all participants signed written informed consent prior to participation. Data from participants that have withdrawn their consent were excluded prior to data delivery from the Tromsø Study. In this thesis, all three studies were approved by the Regional Committee for Medical and Health Research: Paper II was approved by the original approval (2017/1973/REK nord), whereas the approval for Paper I and III was updated (20828/REK nord) due to small changes in the project description (inclusion of Tromsø4 and Tromsø6, and extension of PhD project due to parental leave and the COVID-19 pandemic).

3.4 Assessment of physical activity

In the Tromsø Study, leisure-time PA has been assessed thru three different questionnaires (Figure 4) [115], and by accelerometry in Tromsø7.

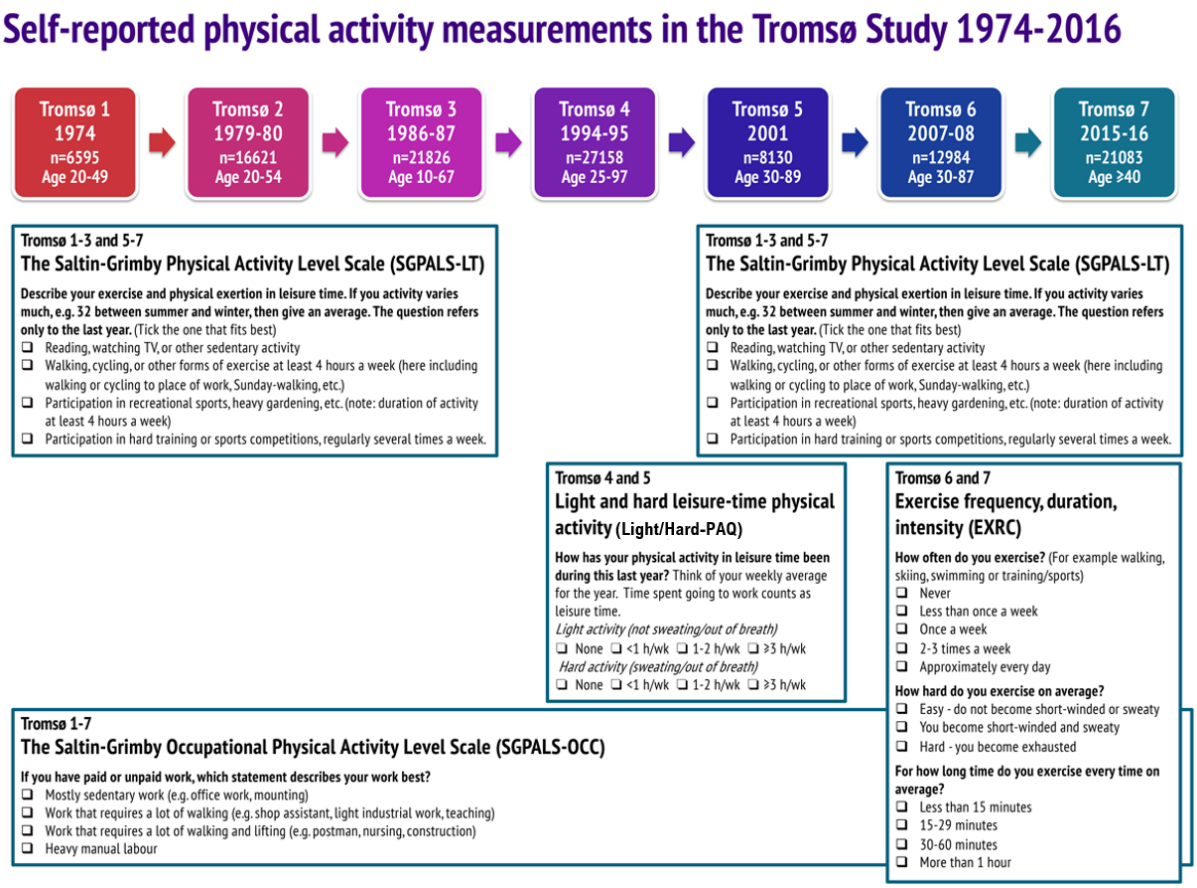

Figure 4. Overview of self-reported measurements of physical activity in the Tromsø Study 1974–2016. Modified from Morseth and Hopstock [115].

3.4.1 The Saltin-Grimby Physical Activity Level Scale

In paper I, PA was assessed using a slight modification of the Saltin-Grimby Physical Activity Level Scale (SGPALS, Figure 4) [116], where the participants rank their average weekly leisure-time PA, over the last year, on a four-level scale. In paper I, we summed up the participants' ranked leisure-time PA in Tromsø6 and Tromsø7 and combined them in a total cumulative score. Furthermore, we divided the cumulative score into three cumulative PA categories: 1) Low (total score 2–3), 2) Moderate (total score 4), and 3) Hard PA (total score 5–8). For sensitivity analyses, we compared the mean PA score in Tromsø6 with the

mean PA score in Tromsø7, stratified by level of cumulative PA (Supplemental Table S1, paper I), to assess whether there were differences in PA score between Tromsø6 and Tromsø7 within each level of cumulative PA. Moreover, the activity level within each level of cumulative PA was quantified with accelerometry-measured PA in Tromsø7 (Supplemental Table S2, paper I).

3.4.2 Accelerometry-measured physical activity

In paper II, PA was assessed by a triaxial accelerometer (wGT3X-BT, ActiGraph LLC, Pensacola, FL, USA). The accelerometer was placed on the participant's right hip, and the participants were instructed by trained research technicians how to wear it, and to perform their daily activities as usual. The participants were instructed to wear the accelerometer day and night for eight consecutive days, except during water-based activities. The accelerations are expressed in triaxial vector magnitude (the square root of the sum of squared activity counts) counts per minute (CPM), and categorized into moderate-to-vigorous PA (MVPA, ≥2690 CPM) based on validated cut-points [117]. Also, the participants' CPM were divided into total PA volume quartiles (Q1=lowest, Q4=highest), with Q1 as reference: Q1 = ≤406 CPM, Q2 = 407–514 CPM, Q3 = 515–634 CPM, and Q4 = ≥635 CPM. Steps were collected from acceleration on the vertical axis based on a proprietary algorithm developed by the manufacturer.

Accelerations from the three axes were collected at 100 Hz aggregated into 10 seconds epochs, and downloaded in the ActiLife software (ActiGraph LLC, Pensacola, FL, USA) with the normal filter. The epoch files from ActiLife were further processed in the Quality Control & Analysis Tool (QCAT), a software developed in MatLab (The MathWorcs, Inc., Natick, Massachusetts, USA). Thereafter, the 10 seconds epochs were summed to 1 minute, and wear time was defined as ≥5 CPM for ≥1 minute at present, or on the proceeding and following 20 minutes. Otherwise, the accelerations were considered and classified as non-wear-time according to the algorithm by Hecht and colleagues [118]. Valid measurements were defined as wear-time ≥10 hours/day for ≥4 days), and all files flagged with invalid wear time were visually inspected to confirm that participants did not have valid wear time [119].

3.4.3 The Light/Hard physical activity questionnaire

In paper III, PA was assessed by the Light/Hard physical activity questionnaire (Light/Hard-PAQ) [120], where the participants rank their weekly average hours over the last year with light

(not sweating or out of breath) and hard leisure-time PA (sweating/out of breath), respectively, on a four-level scale (1: 0 hours/week, 2: <1 hour/week, 3: 1–2 hours/week, 4: ≥3 hours/week (Figure 4). In paper III, we only applied the question about hard PA in the main analyses and characterized them as: 1) 0 hours/week (Inactive), 2) <1 hour/week (Low), 3) 1–2 hours/week (Moderate), 4) ≥3 hours/week (Vigorous). Time spent going to/from work was considered as leisure-time PA. In some analyses, hard leisure-time PA was dichotomized into inactive (0 hours/week; option 1) and active (>0 hours/week; option 2–4). For sensitivity analysis, we combined the questions about light and hard PA into five categories: 1) light and hard PA 0 hours/week (Sedentary), 2) light PA >0 hours/week and hard PA 0 hours/week (Inactive), 3) hard PA 0–1 hour/week (Low), 4) hard PA 1–2 hours/week (Moderate), 5) hard PA ≥3 hours/week (Vigorous).

3.5 Echocardiography

In Tromsø4, echocardiography was performed by a medical doctor trained in echocardiography (n=2717), and the remaining by two expert cardiologists, using a VingMed CFM 750 ultrasound scanner (VingMed Sound A/S, Horten, Norway). In Tromsø6, echocardiography was performed by a qualified sonographer (n=1561), and the remaining by three expert cardiologists, using an Acuson Sequoia C512 (Acuson, Mountain View, California, USA) ultrasound scanner in Tromsø6. In Tromsø7, echocardiography was performed by a single qualified sonographer, using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. The echocardiographic assessments were performed with the use of standard imaging planes in a supine left lateral position for Tromsø4, and the left lateral decubitus position for Tromsø6 and Tromsø7, according to the joint American and European guidelines [121]. In Tromsø4 and Tromsø6, the echocardiographic measurements were performed online in one heart cycle but remeasured if deviating from eye-balled estimates. In Tromsø7, the echocardiographic measurements were performed off-line on 3–5 consecutive cardiac cycles by a physician experienced in echocardiography, and the average was used in the analysis.

3.5.1 Cardiac dimensions and volumes

Dimensions of both LA and LV were measured by M-mode echocardiography in the parasternal short-axis view at the aortic valve level, after alignment of left ventricle in long-axis view, according to the leading edge-to-leading edge convention [121]. LA anteroposterior

diameter was measured at the end of the LV systole and indexed to body surface area (LADi) as cm/m^2. LADi ≥2.3 cm/^{2} was defined as LA enlargement [121]. LV internal dimensions were measured at the end of diastole and systole and indexed to body surface area as cm/m^2 [121]. Relative wall thickness was calculated with the formula: $\frac{(2\ x\ posterior\ wall\ thickness)}{(LV\ internal\ end{-}diastolic\ diameter)}$. LV myocardial mass was calculated according to the cube formula [121], and further indexed to height by raising height to the power of 2.7 (LVMi), and are presented as g/m$^{2.7}$[122].

Both LA and LV volumes were calculated using the Simpson's biplane method from the apical four- and two-chamber views and indexed to body surface area as mL/m^2 [121]. LA volume was measured at the end of the LV systole and indexed to body surface area (LAVi). LAVi ≥34 mL/m^2 was defined as LA enlargement [121]. LV volume was calculated at the end of diastole and indexed to body surface area. Ejection fraction was calculated using the Teichholz formula [123] in paper I and III, and calculated from the end-diastolic and end-systolic estimates of Simpson's biplane calculated LV volumes [121] in paper II.

3.5.2 Doppler examinations

All Doppler examinations were performed in apical four-chamber view. Mitral valve Doppler measurements were performed with a 2mm Doppler sample volume placed between the mitral leaflet tips. Tissue Doppler measurements were performed with a 5mm Doppler sample volume located at the septal and lateral sides of the mitral annulus. Measurement of peak flow velocity in early diastole (E-wave) was measured with pulsed wave Doppler. Mitral annular e' velocity was measured in apical four-chamber view with pulsed wave tissue Doppler in both lateral and septal basal regions and averaged. Average E/e'ratio was calculated by peak E-wave velocity divided by annular average e' velocity both collected in apical four-chamber view. Tricuspid regurgitation velocity was measured as peak modal velocity from the right ventricle to the right atrium during systole, using apical four-chamber view with continuous wave Doppler.

In paper II, mitral stenosis was assessed by pulsed wave mitral valve Doppler. Aortic stenosis was assessed by aortic flow mean pressure gradient by continuous wave Doppler. Mitral regurgitation severity grade was obtained by qualitative estimation of the colour Doppler flow jet area. Pressure half-time of regurgitant aortic flow as well as central jet width were used for

assessment of the severity of the aortic regurgitation [124]. Criteria used to define valvular heart disease in paper I and III are presented in Table 2.

Table 2. Criteria used to define valvular heart disease in paper I and III.

	Diagnosis	Criteria	Reference
Paper I:			
Aortic stenosis	Continuous wave Doppler	Aortic valve mean gradient ≥15 mmHg	[125]
Mitral stenosis	Pulsed wave Doppler	E-wave deceleration time >350 msec and mitral E-wave >1 m/s	[126]
Aortic regurgitation	Colour M-mode Doppler	Vena contracta width >30% of LV outflow tract diameter	[127]
Mitral regurgitation	2D Colour Doppler	regurgitant jet area >4 cm^2	[128]
Paper III:			
Aortic stenosis	Continuous wave Doppler	Aortic valve peak gradient >36 mmHg	[126]
Mitral stenosis	Pulsed wave Doppler	E-wave deceleration time >350 msec and mitral E-wave >1 m/s	[126]
Aortic regurgitation	Colour M-mode Doppler	Vena contracta width >50% of LV outflow tract, or colour jet exceeding mitral valve coaptation point	[127]
Mitral regurgitation	2D Colour Doppler	Regurgitant jet area >7cm^2	[128]

Valvular heart disease was defined if ≥1 of the criteria was met for paper I and III, respectively. 2D, two-dimensional; LV, left ventricular.

3.5.3 Left ventricular diastolic function

LAVi, E/e'ratio, e' velocity, and tricuspid regurgitation velocity were used to consider diastolic function according to current guidelines [32]. In our analysis, LV diastolic function was considered as: a) normal if <50% of the variables were above the cut-offs, or b) abnormal if ≥50% of the variables were above the cut-offs.

3.5.4 Reproducibility

In Tromsø4, intra- and inter-observer variability of the two main observers was evaluated in a subsample of 49 subjects [129]. Both observers examined each subject with one-week intervals.

Inter-observer difference between the two main observers for LA diameter was 0.01 cm (± 0.49 cm), and intra-observer difference was 0.16 cm (± 0.34 cm) [130]. Moreover, inter-observer differences between the two observers were 15.9% for LVMi and 9.1% for ejection fraction. For observer 1, intra-observer differences were 15.8% and 8.8% for LVMi and ejection fraction, respectively. For observer 2, intra-observer differences were 11.9% and 9.5% for LVMi and ejection fraction, respectively.

In Tromsø6, intra- and inter-observer variability on Doppler indices were evaluated by Bland-Altman analysis in 42 participants [125]. The results showed mean inter-observer differences (95% limits of agreement) in the mean aortic gradient of −0.06 mmHg (−3.06 to 3.18). Intra-observer analysis gave a mean difference of −0.04 mmHg (−1.86 to 1.78) and 0.30 mmHg (−3.96 to 4.56), respectively, in the two observers.

In Tromsø7, intra-observer variability was evaluated on Doppler indices in recordings of 30 randomly selected participants with three months intervals between readings [131]. The results showed good- to excellent agreement between measurements, intra-class correlation coefficients on Doppler indices and linear measurements ranged from 0.90 to 0.99.

3.6 Measurements of covariates

In all three papers, we adjusted for baseline covariates extracted from self-reported questionnaires, physical examinations, and blood samples. All data were collected by specially trained research technicians, details about data collection are described elsewhere [112-114].

3.6.1 Data from self-reported questionnaires

In all three papers, the response option was similar for use of antihypertensives (currently, previously/never), myocardial infarction (previously, no), and stroke (previously, no). For diabetes (paper I and III: yes, no; paper II: currently/previously, no), and daily smoking (paper I: yes, previously/never; paper II: currently/previously, never; paper III: yes, no), response option differed slightly between the three papers. Also, questionnaires for alcohol differed between the papers: In paper I, alcohol consumption was the product of two questions, one reporting number of units of alcohol and one reporting frequency of drinking. In paper III, alcohol consumption was summarized from three questions reporting number of

glasses of beer, wine or spirit normally consumed within 14 days. Additionally, data about coffee consumption (cups/day), thyroid disease (yes/no), and palpitations (yes/no) were included for paper III.

3.6.2 Data from physical examinations and blood samples

In all three papers, blood pressure was recorded three times with 1 min intervals after 2 min seated rest with an automatic device (Paper I and II: Dinamap Pro care 300 Monitor, GE Healthcare, Oslo, Norway; paper III: Dinamap Vital Signs 1846 monitor, Criticon, FL, USA); the average from reading two and three was used in our analyses. Thereafter in all three papers, we classified blood pressure into hypertension groups [122]: a) Normotensive (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and no self-reported use of antihypertensives), b) hypertensive, controlled (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and self-reported use of antihypertensives), c) hypertensive, uncontrolled (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and self-reported use of antihypertensives), or d) hypertension, untreated (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and no self-reported use of antihypertensives).

In all three papers, height and weight were measured to the nearest decimal with participants wearing light clothing and no footwear, and body mass index was calculated as weight (kg) divided by height squared (m^2). In paper III, heart rate was recorded three times with 1 min intervals after 2 min seated rest, with an automatic device (Dinamap Vital Signs 1846 monitor, Criticon, FL, USA). The lowest recorded reading was used for resting heart rate.

In paper II, blood samples were analysed for low-density lipoprotein (LDL)-cholesterol at the Department of Laboratory Medicine, University Hospital of North Norway. In paper III, blood samples were analysed for total and high-density lipoprotein cholesterol and C-reactive protein at the Department of Clinical Chemistry, University Hospital of North Norway. LDL-cholesterol was estimated by subtracting high-density lipoprotein cholesterol from total cholesterol.

3.7 Atrial fibrillation registration

The follow-up data on incident AF were derived from the diagnosis registry of the University Hospital of North Norway, the only hospital in the region, by linking the hospital's records of

AF to the participants' unique Norwegian national 11-digit identification number [132]. The participants were followed from the date of examination in 1994-95 (Tromsø4), until a) the date of first documented AF, b) the date of censoring due to death or migration, or c) the end of follow-up on 31 December 2016, whichever came first. Those who had died or emigrated during follow-up were identified through the Population Register of Norway.

AF was detected in digital versions of hospital records using International Classification of Diseases (ICD)-9 codes 427.0–427.99, and ICD-10 codes 147-148. Additionally, in participants with diagnoses of cerebrovascular or cardiovascular events (based on ICD-9 codes 410–414, 428, and 430–438, and ICD-10 codes 120–125, 146, 150, and 160–169), but without diagnosis of arrhythmias, hospital records (until February 2001) were manually searched for notes on AF. The AF events were validated by an independent expert endpoint committee. All AF diagnoses were confirmed by electrocardiography confirmation. Postoperative AF occurring within 28 days after surgery, myocardial infarction, or other acute cardiac events, as well as AF documented the last week of life, were all classified as non-cases.

3.8 Statistical analyses

All statistical analyses were performed using The Statistical Package for Social Sciences (SPSS Inc., IL, USA). Analyses were performed in version 25 (paper II), 26 (paper III), and 28 (paper I) with a two-sided alpha ≤ 0.05 considered statistically significant. In all three papers, descriptive characteristics of the study population are presented as means with standard deviations or percentages with number of observations.

In paper I, we analysed the associations between cumulative PA and change in cardiac structure and function by one-way analysis of covariance (ANCOVA) with Bonferroni adjusted post hoc comparisons. Data on cardiac structure and function are presented as adjusted means with standard error, and effects as adjusted means with 95% confidence intervals (CI) unless otherwise stated. In the main results, we presented the results stratified by sex, as we observed a significant interaction between PA*sex in the association between PA and change in LA diameter ($p=0.024$), whereas no significant interactions were indicated for the other interaction terms. However, given previously reported age differences in LA size, we also stratified our main analyses by age (over/under 65 years). We estimated effect size using two different models: model 1 was unadjusted, model 2 was adjusted for age, sex, body mass index, and hypertension groups. Sensitivity analyses were performed with

smoking, alcohol consumption, diabetes, and LDL-cholesterol stepwise added to model 2. Additional sensitivity analyses were performed excluding participants with known cardiac pathologies (AF, myocardial infarction, stroke, and LV ejection fraction <40%) stepwise.

In paper II, we analysed associations between PA and LAVi, and between enlarged LAVi and indices of LV diastolic function. The associations between quartiles of PA and LAVi were estimated by one-way ANCOVA with a priori comparisons using Q1 as the reference group, and test of linear trend with quartiles of PA treated as a continuous exposure variable. Associations between MVPA or steps and LAVi, and between quartiles of PA and indices of LV diastolic function were estimated by univariable and multivariable linear regression analyses. Data on LAVi are presented as unadjusted means with standard deviations. Effects sizes are presented as differences between group means with 95% CI for quartiles of PA, and unstandardized beta coefficients with 95% CI for MVPA, steps, and for the association between LAVi and indices of LV diastolic function. In the main results, we presented the results stratified by three age groups (40–54, 55-69, ≥70 years), and by LV diastolic function (normal, abnormal) as there was a significant interaction between PA*age (p=0.010) and PA*LV diastolic function (p=0.003) in the association between PA and LAVi, whereas no significant interaction was indicated for the other interaction terms. We estimated effect sizes using two different models: model 1 was unadjusted, model 2 was adjusted for age, sex, body mass index, systolic blood pressure, diabetes, smoking, and LDL-cholesterol. Additional sensitivity analysis was performed with myocardial infarction, heart failure, and valvular heart diseases added to model 2.

In paper III, associations between PA, LA size, and AF risk were evaluated using univariable and multivariable Cox proportional hazard regression analyses. The associations are presented as hazard ratios with 95% CI. The proportional hazard assumption was confirmed by visual inspection of log-minus-log plots. We observed a significant interaction between PA*LA size in the association between PA and risk of AF (p=0.023), whereas no significant interactions were indicated for the other interaction terms. However, given previously reported age and sex differences in the association between PA and AF risk, and between PA and LA size, we also stratified our main analyses by sex and age (over/under 65 years) in addition to LA size. We estimated effect sizes using two different models: model 1 was unadjusted, model 2 was adjusted for age, sex, body mass index, and systolic blood pressure. Additional sensitivity analyses were performed with smoking, coffee consumption, diabetes, LDL-cholesterol,

palpitations, LVMi, thyroid disease, C-reactive protein, alcohol consumption, and resting heart rate stepwise, or jointly added to model 2.

4 Results – summary of papers

4.1 Paper I: Longitudinal associations between cumulative physical activity and change in structure and function of the left side of the heart: The Tromsø study 2007-2016.

The aim of this study was to explore the association between habitual PA over time and change in cardiac structure and function of the left side of the heart, in a general adult and elderly population. The design was longitudinal and based on data from Tromsø6 and Tromsø7. The study included 266 males (61.1 ±8.9 years) and 328 females (58.9 ±9.9 years), ranging from 37 to 76 years, free from valvular heart disease at baseline.

Overall, LADi increased significantly more in the Hard compared to the Moderate PA group (0.08 cm/m^2, 95% CI 0.01–0.15) from Tromsø6 to Tromsø7. However, when stratified by sex or age, higher levels of cumulative PA were associated with increased LADi in males and in participants <65 years only. Overall, LVMi increased significantly more in Moderate than in Low PA (3.9 g/$m^{2.7}$, 95% CI 0.23–7.57). However, when stratified by sex or age, the change in LVMi was only significant in females. No significant associations were observed between cumulative PA and change in relative wall thickness, E/e' ratio, e' velocity, LV ejection fraction, and ratio between LADi and LV diameter index.

In conclusion, higher levels of habitual PA over time were associated with increased LADi in males and participants <65 years, and with increased LVMi in females. Despite cardiac chamber enlargement, indices of the pump function of the heart did not change with higher levels of PA, and the atrioventricular ratio was unchanged. Our results indicate that cardiac chamber enlargement is a physiological response to PA.

4.2 Paper II: Cross-sectional associations between accelerometry-measured physical activity, left atrial size, and indices of left ventricular diastolic dysfunction: The Tromsø Study.

The aim of this study was to explore the association between accelerometry-measured PA and LA volume in a general adult and elderly population. Furthermore, we aimed to explore if LA enlargement was adversely associated with indices of LV diastolic dysfunction when adjusting for PA. The design was cross-sectional and based on data from Tromsø7. The study included 758 males (65.6 ±10.5 years) and 815 females (63.5 ±10.9 years), ranging from 40 to 84 years.

We observed significant associations between PA and LAVi at ages <70 years, and in participants with normal diastolic function, whereas no associations were seen at ages ≥70 years or for participants with abnormal diastolic function. The most active participants at age 40–54 years (4.45 mL/m^2, 95% CI 0.82–8.08) and 55–69 years (2.93 mL/m^2, 95% CI 0.46–5.41) had larger LAVi compared to the least active in their respective age group. LAVi enlargement was only associated with indices of LV diastolic dysfunction in the most inactive participants.

In conclusion, higher levels of PA were associated with greater LAVi in participants <70 years with normal LV diastolic function. LAVi enlargement was only associated with LV diastolic dysfunction in the most inactive participants.

4.3 Paper III: Associations between physical activity, left atrial size and incident atrial fibrillation: the Tromsø Study 1994-2016.

The aim of this study was to explore the role of PA in the association between LA size and incident risk of AF in a general adult and elderly population. The design was prospective and based on data from Tromsø4. The study included 1181 males (57.7 ±10.7 years) and 1298 females (59.3 ±10.7 years), ranging from 25 to 83 years, free from known cardiac pathology. Of these, 399 participants (214 males and 185 females) were diagnosed with AF during a mean follow-up of 16.6 ±6.6 years (median 20.2 years, interquartile range 11.6–21.9 years).

We observed a U-shaped relationship between PA and AF, and moderately active had 32% lower AF risk than inactive (HR 0.68, 95% CI 0.50–0.93). Participants with LA enlargement had 38% higher AF risk compared with participants with normal LA size (HR 1.38, 95% CI 1.12–1.69). However, the increased AF risk with LA enlargement was attenuated by PA; compared with inactive participants with LA enlargement, the AF risk was 45% lower among active with LA enlargement (HR 0.55, 95% CI 0.39–0.79). Moreover, AF risk in active participants with LA enlargement did not differ from active with normal LA size (p=0.938). These patterns were also observed in sex and age-stratified analyses.

In conclusion, Moderate PA was associated with reduced AF risk, and PA attenuated the increased risk of AF with LA enlargement in both sexes and age groups.

5 Discussion of methodology

5.1 Validity

Validity is related to how trustworthy the results we observe are, either in relation to the study sample (internal validity) or whether the results are generalisable to other populations not participating in the study (external validity) [133,134]. Thus, external validity depends on internal validity, and if the results are not valid for the study population, external validity of the study results is not relevant. Therefore, in order to evaluate whether our results might fill knowledge gaps and be generalised to other populations, it is of importance to discuss the validity of the study results.

Internal validity depends on the methods used to select participants, collect relevant data, and conduct analyses [133]. Therefore, observed associations between exposure and outcome may be true, but may also be due to other possible explanations (chance, bias, or confounding), which all threaten the results' internal validity [134]. Chance, as a possible explanation for the observed associations, is handled with statistical probability theories and suitable statistical methods, as presented in chapter 3.8. Thus, in the following sections, risk of potential bias and confounding are acknowledged and discussed in relation to the studies of this thesis.

5.2 Selection bias

Bias is the result of systematic error in the design or conduct of a study [135], and validity refers to the degree that bias is absent [135]. Several types of bias have been described [136], but most biases in epidemiology can be classified into two main categories *selection-* and *information bias* [135,136].

Selection bias occurs when we have a systematic error in the recruitment or retention of participants, resulting in erroneous associations between exposure and outcome [135]. Selection bias may result from the subcategories *population bias* or *response bias* [136]. However, selection bias generally does not influence the internal validity of the study population, but it may threat the external validity to other populations [133]. Thus, it is of importance to discuss whether the external validity of our results has been weakened by selection bias.

5.2.1 Population bias

Population bias is affected by how the study participants are identified and recruited (e.g., social media, or newspapers etc.), as some participants may not receive invitation in certain information channels [136]. Also, population bias may be caused by choice of study population (students, volunteers, or ethnicity), as different populations may differ in behaviour and health status [136].

The Tromsø Study cohort largely consists of Caucasians of Norwegian origin (85%) [113,114]. Moreover, 80% of the inhabitants live in urban areas, and residents mainly work within tertiary industry, whereas a lesser proportion is employed in secondary- or primary industry [114]. Thus, the Tromsø Study cohort may be considered representative of a Northern Europe Caucasian urban population [114].

The Tromsø surveys aim to include large representative samples of the Tromsø population, and consist of a combination of whole birth cohorts, and random samples of other birth cohorts predefined and based on scientific basis before the study start [112]. Thus, selection bias is reduced as the population was selected randomly. Furthermore, in the Tromsø Study, all inhabitants were identified by the official population registry, and a personal informed invitation was mailed about two weeks ahead of a suggested time of appointment [112]. Moreover, to facilitate individual preferences, the subjects were free to attend whenever suitable during the period of data collection of the study (~1 year). Non-attendees were reminded one time. Thus, the probability of selection bias due to participants not receiving invitation is likely minimal.

5.2.2 Response bias

Response bias may be introduced as non-attendees tend to differ from attendees. In general, non-attendees have lower socioeconomic status, are more prevalent smokers, have a less healthy lifestyle, have a higher prevalence of chronic diseases, and have higher risk of cardiovascular disease and mortality than attendees [115,137]. Moreover, non-attendees tend to be males, unemployed, and single [138]. Unfortunately, due to legal restrictions from the Norwegian Data Inspectorate, detailed descriptive analyses of the non-attendees in the Tromsø Study are impossible [112]. However, compared with subjects who were consistent attendees, age- and sex-adjusted mortality was higher among subjects who had attended only once despite several invitations [112].

Attendance was relatively high for the surveys used in this thesis: Tromsø4 (77% attendance), Tromsø6 (66% attendance), and Tromsø7 (65% attendance). The relative high attendance reduces the degree of potential selection bias, but still, the external validity to young single males, especially those with low socioeconomic status, comorbidities, and less healthy lifestyle, is probably weaker in the Tromsø Study. Therefore, the beneficial effect of PA on AF risk was probably underestimated in paper III, as the analytical sample likely was biased towards a healthier population.

In paper I and II, baseline characteristics were similar between our analytical samples and the total cohort attending visit 1 in Tromsø6 (Table 3) and Tromsø7 (Table 4). However, in paper I, the analytical sample was slightly older, healthier and had fewer smokers compared with the total cohort attending Tromsø6. For paper II, the analytical sample was older (64.5 vs 57.3 years), and correspondingly had slightly higher blood pressure and prevalence of comorbidities than the total cohort attending Tromsø7. Overall, these slight differences are unlikely to induce severe selection bias, and we consider the analytical samples representative of the Tromsø Study cohort. This strengthens the external validity of our results to other adult and elderly Northern European Caucasian urban populations.

Table 3. Generalisability of the analytical sample in paper I: The Tromsø Study 2007–2008

Baseline characteristics	**Analytical sample**	**Attended visit 1, Tromsø6**
Age, years	60.0 (9.6)	57.5 (12.7)
Sex, % (n) female	55.2 (328)	53.4 (6928)
Body mass index, kg/m^2	26.7 (4.0)	26.9 (4.3)
Systolic blood pressure, mmHg	137.7 (21.6)	135.6 (23.0)
Diastolic blood pressure, mmHg	78.2 (10.2)	77.8 (10.7)
Resting heart rate, beats/min	64.0 (9.2)	65.4 (10.6)
LDL-cholesterol, mmol/L	3.6 (1.0)	3.6 (1.0)
Heart attack, % (n)	4.8 (28)	5.4 (682)
Stroke, % (n)	1.9 (11)	2.9 (362)
Atrial fibrillation, % (n)	2.0 (12)	3.3 (429)
Ejection fraction <40%, % (n)	0.2 (1)	0.6 (12)
Diabetes, % (n)	4.4 (26)	5.0 (634)
Smoking, % (n)	16.4 (97)	20.4 (2610)
Alcohol, units/month	10.1 (11.9)	9.6 (12.5)

Numbers are mean ±standard deviation or percentage and n. LDL: low-density lipoprotein.

Table 4. Generalisability of the analytical sample in paper II: The Tromsø Study 2015–2016

Baseline characteristics	**Analytical sample**	**Attended visit 1, Tromsø7**
Age, years	64.5 (10.7)	57.3 (11.4)
Sex, % (n) female	51.8 (815)	52.5 (11074)
Body mass index, kg/m^2	27.1 (4.3)	27.3 (4.5)
Systolic blood pressure, mmHg	134.3 (20.5)	129.6 (19.8)
Diastolic blood pressure, mmHg	75.1 (10.0)	75.4 (10.1)
LDL-cholesterol, mmol/L	3.5 (1.0)	3.6 (1.0)
Heart attack, %	6.8 (105)	3.7 (753)
Stroke, % (n)	3.5 (54)	2.7 (547)
Diabetes, % (n)	6.9 (109)	5.5 (1124)
Smoking, % (n)	12.0 (189)	13.9 (2904)

Numbers are mean ±standard deviation or percentage and n. LDL: low-density lipoprotein.

In paper III, participants attending visit 2 were older than the total cohort attending visit 1 in Tromsø4, as about 90% of the invited were >50 years, whereas only a 5–8% random sample of the other age groups aged 25–85 years were invited [112]. However, baseline characteristics for the analytical sample were similar, but the analytical sample was slightly healthier regarding diabetes, stroke, and hypertension, than the total cohort attending visit 2 in Tromsø4 (Table 5). Nevertheless, the analytical sample generally represents participants >50 years in the Tromsø Study cohort, which strengthens the external validity to other adult and elderly Northern European Caucasian urban populations >50 years.

Table 5. Generalisability of the analytical sample in paper III: The Tromsø Study 1994–1995

	Analytical sample	Attended visit 2, Tromsø4	Attended visit 1, Tromsø4
Baseline characteristics			
Age, years	58.6 (10.7)	60.3 (10.1)	46.9 (15.1)
Sex, % (n) female	52.4 (1298)	50.7 (3465)	52.6 (14138)
Body mass index, kg/m^2	25.8 (3.8)	26.0 (4.0)	25.2 (3.9)
Systolic blood pressure, mmHg	143.1 (21.8)	145.2 (22.5)	134.8 (20.5)
Diastolic blood pressure, mmHg	82.6 (12.4)	83.4 (12.9)	78.1 (12.4)
Resting heart rate, beats/min	70.6 (12.2)	71.0 (12.6)	70.3 (12.2)
LDL-cholesterol, mmol/L	5.1 (1.3)	5.2 (1.3)	4.5 (1.3)
C-reactive protein, mg/L	2.6 (6.5)	2.8 (6.8)	2.8 (6.9)
Antihypertensives, % (n)	10.3 (253)	13.6 (925)	6.2 (1662)
Hypertension, controlled, % (n)	1.7 (42)	2.6 (177)	1.3 (357)
Hypertension, uncontrolled, % (n)	8.5 (211)	11.0 (748)	4.9 (1304)
Hypertension, untreated, % (n)	44.7 (1109)	46.0 (3130)	29.6 (7939)
Stroke, % (n)	1.7 (42)	2.7 (186)	1.5 (414)
Diabetes, % (n)	2.2 (54)	3.2 (216)	1.8 (480)
Palpitations, % (n)	22.8 (494)	25.0 (1483)	23.2 (5336)
Thyroid disease, % (n)	5.5 (119)	5.6 (325)	3.5 (788)
Smoking, % (n)	31.3 (775)	31.7 (2166)	36.1 (9698)
Alcohol, glasses/14 days	4.2 (6.5)	4.1 (6.2)	4.9 (6.4)
Coffee, cups/day	5.5 (3.4)	5.5 (3.3)	5.3 (3.8)
Physical activity [a]			
Inactive, % (n)	60.6 (1502)	64.2 (4339)	49.3 (13167)
Low, % (n)	15.4 (383)	14.4 (974)	20.4 (5455)
Moderate, % (n)	15.8 (391)	14.2 (957)	19.9 (5324)
Vigorous, % (n)	8.2 (203)	7.3 (491)	10.3 (2759)
Follow-up characteristics			
AF during follow-up, % (n)	16.1 (399)	19.0 (1300)	6.6 (2424)
Follow-up time, years	16.6 (6.6)	15.4 (7.5)	16.9 (7.3)

Numbers are mean ±standard deviation or percentage and n. PA: physical activity, LDL: low-density lipoprotein, AF: atrial fibrillation.

[a] = Hard leisure-time PA, weekly average over the last year.

5.3 Information bias and misclassification

In epidemiology, information bias is a significant threat to the internal validity of a study, and results from either imperfect definition of study variables or erroneous procedures of data collection may lead to misclassification of both exposure and response variables in a significant proportion of participants [135]. Misclassification errors may be systematic

(differential misclassification bias), when the probability of being misclassified differs between the groups in a study, or random (non-differential misclassification), when the probability of individuals being misclassified is similar across all groups in a study [133,136]. Non-differential measurement errors are unavoidable, usually due to inaccurate measurements, and often overlooked as the errors often cancel each other out [136]. However, whereas non-differential misclassification errors generally weaken the association and lower the relative risk between exposure and outcome [136], differential misclassification may dilute or strengthen an association [135].

Typical sources of misclassification errors in epidemiology include measurement errors [136], which are often due to recall bias, and investigator bias (interviewer and observer bias) [135].

5.3.1 Recall bias

Recall bias results from inaccurate recall of past exposure, which results in misclassification of exposure status and biased study results [135]. Whereas non-differential misclassifications due to inaccurate recall of past exposure would weaken the associations [136], recall bias may result from social desirability bias, where people tend to underreport social undesirable responses (e.g., smoking and alcohol consumption) and overreport socially desirable responses (e.g., PA level) [139].

Thus, self-reports are prone to both recall- and social desirability bias, and measures of self-reported PA are generally unprecise and overestimated in questionnaires [140,141]. Hence, the true effect of PA on outcomes (e.g., AF) is likely underestimated in studies based on self-reports. In contrast, device-based measures are less prone to recall- and social desirability bias [135], and devise-based PA assessment is, therefore, more valid and reliable compared to self-reports [140]. In paper II, PA was assessed by accelerometry, whereas it was considered by self-report in paper I and III. The validity of accelerometry- and self-reported PA will be discussed in chapters 5.3.3 and 5.3.4.

Furthermore, data regarding comorbidities (myocardial infarction, stroke, diabetes, thyroid disease, palpitations, and use of antihypertensives), smoking, alcohol, and coffee consumption were all assessed by self-reports. However, self-reported data on comorbidities are probably relatively valid, as the participants know if they have been hospitalised, or if the doctor has medicated them for the morbidities. In contrast, data on palpitations are subjective and

probably less valid. However, data on palpitations were only used in a sensitivity analysis in paper III but did not affect the effect estimates. Furthermore, data on alcohol consumption and smoking habits were probably underestimated due to social desirability bias. However, alcohol consumption and smoking were only used in sensitivity analysis in paper I and III without influencing the effect estimates. In paper II, smoking was included in the multivariable-adjusted model and could, therefore, potentially have led to underestimation of the association between PA and LAVi if some smokers were treated as non-smokers.

5.3.2 Investigator bias

Errors at the data collection stage may lead to misclassification of outcome status [135]. Differential misclassification may occur if the ascertainment of outcome is influenced by the knowledge of exposure status, especially if the outcome is subjective [135]. Attempts to prevent investigator bias include development of a detailed test manual, training of staff, blinding interviewers from exposure status, and standardisation of data collection procedures [135]. In the Tromsø Study, all data were collected by specially trained research technicians [113,114], which were blinded from the study aims as the data collection was performed before the study aims in this thesis were developed. Moreover, all examinations, measurements, and laboratory work followed standardised protocols [113], and objective measures were used for physical examinations and blood samples. Also, the cut-off values for cardiac chamber quantification [121], valvular heart disease [126-128], LV diastolic function [32], blood pressure [122], and body mass index [142] were based on international recommendations. Thus, the risk of investigator bias through unprecise and/or subjective ascertainment was reduced, which strengthen the internal validity of our results.

The most efficient approach to avoid misclassification bias is by use of objective markers of exposure (e.g., accelerometry-measured PA), and accurate diagnostic techniques for ascertainment of outcome (e.g., 12-lead electrocardiography for AF diagnosis, and two-dimensional echocardiography for heart structure and function) [135]. However, measurement error may occur if numerous technicians collect the same variables differently, or due to the accuracy of the equipment [136]. Therefore, methodological considerations of PA assessments, echocardiography, and AF are discussed in the following sections (5.3.3–5.3.6).

5.3.3 Accelerometry-measured physical activity

Accelerometry-measured PA is less prone to recall- and social desirability bias than self-reports [135,143], and has been proved more accurate than self-reported questionnaires against the doubly labelled water technique [144]. However, the accelerometers are also prone to potential measurement error and bias that should be acknowledged.

Firstly, PA should ideally be assessed during daily life and over a long period of time to be representative of the participants' habitual PA level [145]. However, increasing the criteria for number of valid days and hours required for valid wear time may decrease sample size and study power [146]. Usually, 3–5 days of accelerometer monitoring is required to reliably estimate habitual PA [147]. Moreover, Matthews and colleagues demonstrated that 3–4 days of uniaxial PA monitoring were needed to reach 80% reliability, and that 7 days of monitoring resulted in 90% reliability in both males and females [148]. In accordance with this, the participants in the Tromsø Study were instructed to wear the triaxial accelerometer for seven days, with a set minimum of four valid days with minimum of 10 hours wear time. Our sample's average wear time was 17.2 hours/day for 6.8 days.

Second, in line with the Hawthorne effect [149], accelerometer reactivity may potentially induce information bias due to higher activity levels on day one compared with the following days [150]. To control for this, the accelerometer was set to start recording at midnight the same day the accelerometer was attached [119]. However, we cannot rule out that potential uncontrolled reactivity has biased (overestimated) the participant's PA level.

Third, the count-based cut-points we used to define MVPA were based on a laboratory study of males and females (~28 years, ~72 kg, ~173 cm) [117]. In contrast, the study population in paper II was older (~65 years), heavier (~78 kg) and slightly shorter (~170 cm) than the reference group. Thus, the applied cut-point for MVPA could potentially induce misclassification (underestimate MVPA in the elderly), as the cut-points were not calibrated for the higher age of our study population [151]. However, based on similar anthropometry between the reference group and our analytical sample, the cut-points should be reasonably accurate for our study population at the population level. Moreover, MVPA is defined by the number of counts needed to achieve ≥3 metabolic equivalents (i.e., oxygen consumption of ≥10.5 mL/kg/min), which corresponds to walking the dog or picking fruits of trees, or higher intensities [152]. Furthermore, average maximal cardiorespiratory fitness among males (n=300)

and females (n=240), aged 60–69 years, from the population-based Nord-Trøndelag Health Study was 39.2 and 31.1 mL O_2/kg/min, respectively [153]. Thus, achieving MVPA is presumably reasonably obtainable in our study population, despite higher age, lower fitness, and different body composition than the reference group.

A strategy to avoid potential misclassification (investigator bias) due to count-based cut-points, is to divide into PA levels from CPM on a continuous scale (e.g., PA-quartiles of total CPM). However, a limitation with this volumetric approach is that information about intensity is removed, as a high number of CPM could be due to both high volume of light PA, or high volume of MVPA. Thus, combining count-based cut-points and PA levels defined from a continuous scale would probably be more informative. Another limitation with the count-based cut-points, is that it is based on oxygen consumption during treadmill running and walking. Thus, the energy cost of other activities (e.g., cycling or strength training) might be underestimated due to different movement patterns [145,154].

Fourth, due to the biomechanics of running, a plateau in activity counts is seen with higher intensities, where activity counts plateaued at approximately 10 km/h treadmill run, and tended to decrease with even higher intensities [155,156]. Thus, the inability of the ActiGraph-monitor to record higher intensities of exercise underestimates the amount of vigorous PA, and accordingly, total CPM [155]. However, at a population level, it is unlikely that the inability to record running >10 km/h, constitutes a significant issue.

Fifth, the classification of non-wear time constitutes risk of potential misclassification bias. The Hecht algorithm [118] was initially developed for assessment of PA in chronic obstructive pulmonary disease patients using a different triaxial accelerometer. However, validated against a dataset using two accelerometers and electrocardiogram recordings, the Hecht algorithm has similar accuracy in detecting non-wear time as the Troiano algorithm [157], based on 11196 children, adolescents, and adults using a uniaxial ActiGraph-accelerometer. However, both the Hecht and the Troiano overestimated the amount of non-wear time in the data [158]. Thus, our participants probably have some sedentary wear time misclassified as non-wear time, and the total CPM is somewhat underestimated. However, MVPA is probably not affected as our applied cut-off for MVPA (≥2690 CPM) is significantly higher than the ≥5 CPM cut-off applied in the Hecht algorithm.

5.3.4 Self-reported physical activity

The SGPALS has shown high reliability, with a Kappa value of 0.69 with 4–6 weeks apart [159], and 86% agreement one month apart [160]. Similarly, Emaus and colleagues demonstrated an intra-class correlation of 0.86 using data from Tromsø6 [161].

Furthermore, Emaus and colleagues validated the SGPALS against maximal cardiorespiratory fitness in a sub-study of Tromsø6, and found moderate correlations (r_s 0.40 and 0.44) for females and males, respectively [161]. Moreover, the SGPALS has good discriminative ability in terms of ranking an individual's maximal cardiorespiratory fitness (37, 42, 46, and 46 mL O_2/kg/min, respectively) [161]. Similarly, when the SGPALS was compared to accelerometry-measured PA, the correlation was weak (r_s 0.25–0.28) [161], but showed good discriminative ability in terms of ranking MVPA (28, 35, 47, and 72 minutes of daily MVPA, respectively) [161]. Correspondingly, a modified version of SGPALS demonstrated a good correlation with accelerometry-measured PA (r_s 0.64), and showed good discriminative ability in ranking MVPA [162]. Thus, these results indicate that the SGPALS reflects aerobic exercise and MVPA, and can be used for ranking and categorising participants into PA levels. Similarly, in our sensitivity analysis of the cumulative PA categories in paper I (Supplementary Table S2, paper I), the cumulative PA categories discriminated between accelerometry-measured MVPA (20, 36, 48 minutes of daily MVPA, respectively), and steps (4690, 6510, 7598 steps per day, respectively).

Furthermore, Aires and colleagues demonstrated that the ranking of PA level by the SGPALS could discriminate between different levels of blood lipids and body mass index [163]. Moreover, the SGPALS may predict the risk of cardiovascular diseases [164], including AF [93,94,165], and cardiovascular- and all-cause mortality [166,167].

The Light/Hard-PAQ has been validated in 108 randomly selected men aged 20–39 years [120], and the question concerning hard PA has acceptable test-retest reliability (r_s=0.50) measured one week apart. Also, the hard PA questionnaire has acceptable validity against maximal cardiorespiratory fitness (r_s=0.46), and accelerometry measured vigorous PA (r_s=0.31) [120]. Thus, the Light/Hard-PAQ concerning hard leisure-time PA is likely a better measure of MVPA than total activity [120]. Moreover, the Light/Hard-PAQ has good discriminative ability in ranking an individual's maximal cardiorespiratory fitness (42, 44, 47, and 51 mL O_2/kg/min, respectively) [120]. Also, the Light/Hard-PAQ may predict risk of acute coronary

heart disease [168]. Moreover, the Light/Hard-PAQ has been used in prediction models of estimated cardiovascular fitness, and may predict risk of acute myocardial infarction [169], AF [170], and cardiovascular- and all-cause mortality [171].

Overall, both questionnaires are prone to recall- and social desirability bias. This might result in potential overestimation of PA due to differential measurement error, and also underestimation of the associations between PA and heart structure and function, and AF, due to non-differential measurement error.

5.3.5 Echocardiography

Cardiac magnetic resonance imaging is considered the gold standard for structural assessment of cardiac chambers and mass due to high spatial resolution and three-dimensional data provision [15]. However, cardiac magnetic resonance imaging is also time-consuming and expensive [172], and therefore less suited for epidemiological studies. In contrast, the wide availability, ease of use, large body of normative data, and prognostic value make two-dimensional echocardiography a clinically powerful tool well-suited for epidemiological research [121,173]. However, compared with cardiac magnetic resonance imaging, two-dimensional echocardiographic atrial and ventricular dimensions and volumes are typically smaller, whereas wall thickness and mass are larger [121,174].

Anteroposterior LA diameter has been used extensively in clinical practice, and is the most used linear measurement of LA size, largely as it traditionally was the most reproducible measurement [121]. Furthermore, anteroposterior LA diameter has shown higher intra-class coefficients and precision compared to LA volume by the Simpson's biplane method [175]. Therefore, LA diameter is appropriate for longitudinal analyses with repeated measures, such as in paper I. Moreover, LA diameter has prognostic value of several cardiovascular outcomes [176,177], including incident risk of AF [35,74], and mortality [178]. However, anteroposterior LA diameter has several geometric assumptions, and assumes that all dimensions change similarly when the left atria enlarge [121]. This is not always the case during LA remodelling [121], and the dilation of the left atria may also be limited in the anteroposterior dimension due to the spine and the sternum [179,180]. In contrast, LA volume has fewer geometric assumptions than linear dimensions, as it considers atrial chamber enlargement in all dimensions, and is therefore the recommended measurement of LA size [121]. Furthermore, LA volume has strong prognostic value for several cardiac pathologies [121,181,182], and LA volume is more sensitive in

detecting LA enlargement [183], and a stronger predictor of cardiovascular outcomes than anteroposterior LA diameter [121,176].

The echocardiographic sampling by several technicians collecting data might facilitate measurement error in paper I and III: In paper I, four observers collected the echocardiography data. However, 68.5% of the participants were assessed by the same observer, which may reduce the risk of measurement error. Moreover, in a reproducibility study, mean inter-observer differences in the mean aortic gradient were minor between the two main observers. Other echocardiography variables were not evaluated. In paper III, three medical doctors collected the echocardiography data; however, as 82% of the participants were assessed by the same observer, this may reduce the risk of measurement error. In a reproducibility study, the inter-observer difference between the two observers for LA diameter was small, whereas the intra-observer difference was somewhat larger [130]. Moreover, the inter-observer coefficient of variance between the two main observers was 15.9% for LVMi and 9.1% for LV ejection fraction [129]. Despite some intra-/inter-observer disagreement, there was no systematic variation in the measurements [129]. As most of the participants were assessed by the same observer, the non-differential measurement error likely did not induce severe information bias.

Consequently, the true association between PA and change in LA size (paper I), and between LA size and AF risk (paper III), are potentially underestimated due to several observers, and due to the ability of LA diameter compared with LA volume in detecting enlargement. Thus, use of LA volume measurements, and a single observer, could potentially have strengthened these associations.

5.3.6 Atrial fibrillation ascertainment

The internal validity (specificity) of AF ascertainment is strong as AF was hospital-confirmed by 12-lead electrocardiography [50]. In contrast, data from the Tromsø Study has estimated sensitivity of 70% for self-reported AF compared with hospital-confirmed AF by 12-lead electrocardiography [184]. However, the true prevalence of AF is likely somewhat underestimated, as some participants with silent paroxysmal AF were in sinus rhythm at examination and thus misclassified as non-cases. Moreover, it is highly likely that some AF patients are never hospitalised due to lack of symptoms. However, assuming that these misclassifications are non-differential, the incidence of AF was probably proportionally

higher in the inactive or diseased population than in the active population, leading to underestimation of the beneficial effects of PA on AF risk.

5.4 Confounding

The term confounding refers to situations where a non-causal association between exposure and outcome is observed due to the influence of a third variable, or group of variables, known as confounders [135]. There are no variables that are intrinsic confounding variables themselves [136], but confounders are variables that are related to both the exposure and the outcome [135]. Common strategies to control confounders include randomisation, matching of subjects, restriction of selection criteria, stratification, and statistical adjustments for potential confounders in multivariable models [136].

However, matching and randomisation were impossible as the papers constituting this thesis were performed on already collected observational data. Thus, we had to control for confounding by stratification and/or statistical adjustment of potential confounders in our analyses. Variables treated as confounders were found through literature reviews. However, we cannot exclude residual confounding due to unmeasured variables (e.g., silent AF, masked hypertension, or genetics), or due to measurement errors of measured variables [136]. Thus, despite adjustment for multiple potential confounders, we cannot rule out residual confounding as an alternative explanation of the observed associations between PA and cardiac structure and function, and risk of AF.

Imperfect adjustment of confounding by imprecise ascertainment of covariates may result in residual confounding [135]. Thus, the adjusted estimates of the association between PA and heart structure and function may have been misclassified. If the misclassification of the confounders were non-differential, the associations were biased towards the null hypothesis [135]. If the misclassification of confounders were differential, the associations might dilute or strengthen [135].

5.5 Study design

In paper I, we applied a longitudinal design with repeated measures of PA and echocardiographic structural and functional data. The main strength of the study design is the repeated measures which enable evaluation of the direction of the associations. The main

limitations are the self-reported PA, use of linear dimensions instead of volumes, and the relatively small sample size.

In paper II, we applied a cross-sectional design to investigate the association between PA and LA size. The main strength of the study design is the use of devise-based PA in combination with LA volume, and a large study population with a wide age span. The main limitation is the cross-sectional design; thus, we cannot prove the direction of the association.

In paper III, we applied a prospective design to investigate the association between self-reported PA, LA size, and risk of AF. The main strength of this study design is the long follow-up for hospital-diagnosed AF in combination with echocardiography data. Thus, we may explore the risk of AF associated with different levels of PA and LA size. The main limitation is the use of self-reported PA and anteroposterior LA diameter instead of LA volume.

A common strength for all three papers is the broad diversity of covariates, allowing us to adjust for multiple potential confounders. However, residual confounding by measured, or unmeasured variables, constitute potential limitations to the studies.

5.6 Causation

If we had successfully accounted for confounding in addition to chance, bias, and measurement error in an association between exposure and outcome, a causal relationship is what remains [136]. However, due to the nature of epidemiological studies, they are prone to potential bias, residual confounding, measurement error, and chance. Thus, the relationship between an exposure and outcome may reflect associations, but not necessarily causal relations.

In 1965, Sir Austin Bradford Hill presented nine viewpoints for evaluating epidemiologic data for causation [185]. More recently, Bhopal [136] and Szklo [135] have published modified versions of Hill's viewpoints, for epidemiology, where Szklo [135] argues that *coherence, analogy*, and *specificity* are not valuable in the discussion of causality. However, none of Hill's viewpoints can demonstrate causation, but the use of them could be useful in revealing study weaknesses [185]. Similarly, Bophal argues that these viewpoints should not be used as a checklist for causation [136], but that it might be useful to synthesise them to strengthen our conclusions [136],

or to reveal lack of evidence for causation and thereby highlight the need for further research [136].

6 Discussion of results

The main findings of this thesis are that exercise-induced cardiac remodelling also occurs with moderate levels of habitual PA, and not only in endurance-trained athletes. Moreover, our results indicate that exercise-induced LA remodelling is a benign physiological adaptation to exercise, without being associated with LV diastolic dysfunction or increased risk of incident AF.

In paper I, we observed that higher levels of cumulative PA were associated with increased LA size in general, and increased LV size in females. However, no change in pump function or atrioventricular ratio at rest was observed with higher levels of PA. In paper II, albeit cross-sectional, the positive association between PA and LA size was confirmed in a subpopulation of the cohort with accelerometry-measured PA and measures of LA volume. LA enlargement was associated with indices of LV diastolic dysfunction in the least active quartile of individuals only. In paper III, we observed that LA enlargement was associated with higher risk of AF compared with participants with normal LA size. However, this did not apply to active individuals with LA enlargement, who did not have higher risk of AF than neither active nor inactive with normal LA size. Furthermore, inactive with LA enlargement had considerably higher risk of AF than all other groups.

The results are discussed thoroughly in the respective papers, and the following discussion will therefore address aspects related to causation, which is an important issue in epidemiological research due to the observational design. Therefore, in the following, the results from paper I–III will be discussed in light of six of Hill's viewpoints [185]:

1) Strength of the association
2) Dose-response
3) Consistency
4) Experimental confirmation
5) Temporality
6) Biological plausibility

6.1 Strength of the association and dose-response relationship

The greater the strength of the association, the more likely the association is to be causal, as it is less likely to be influenced by bias or confounding [135]. Nevertheless, a weak association does not exclude the possibility of causation [135]. Moreover, if the strength of the association varies with level of exposure, we have a dose-response relationship [136]. A linear dose-response relationship is considered strong evidence for a cause-effect relationship to exist, as confounding or bias generally have less explanatory value when there is a linear dose-response relationship [135]. However, a causal dose-response relationship may also be characterised by other shapes of the dose-response curve, due to the biological nature of the mechanisms underpinning the relationship (e.g., U-shaped curve) [135].

Adjusted for multiple cardiovascular risk factors, we observed strong associations between level of PA and LA size in paper I and II. In paper I, LA size in the most active group increased 53% (0.9 cm/m^2) more than in the moderate group over time, and 44% (0.8 cm/m^2) more than in the least active group. In paper II, the most active quartile had 16% (4.45 mL/m^2) larger LA volume than the least active quartile among those aged 40–54 years. Furthermore, the dose-response relationship between levels of cumulative PA and cardiac remodelling (paper I), and the linear relationship between minutes of MVPA, or number of steps, or quartiles of total CPM, and LA size (paper II) strengthens the observed association between PA and LA size in the thesis.

In paper III, we observed that the risk of AF was 32% lower among moderately active compared to inactive, and a U-shaped dose-response curve was seen, where the protective effect of PA diminished with the highest level of PA. Furthermore, participants with LA enlargement had 38% higher risk of AF than participants with normal LA size. However, the AF risk with LA enlargement was attenuated by PA, and active participants with LA enlargement had 45% lower AF risk than inactive with LA enlargement without having higher risk than those with normal LA size.

Thus, the strong associations that varied with level of exposure strengthen our results, and the case for causal relations is possible for all three papers.

6.2 Consistency with previous research

Consistency of results across epidemiological studies is considered a guideline to infer causation in observational studies, although consistency among studies also may be due to consistency of confounding or bias across studies, or due to publication bias [135]. However, causal effects usually are widely applicable, whereas spurious associations often are local [136]. Thus, consistent results across different populations would strengthen the probability of a causal relationship. In this section, our main results are discussed in light of previous research.

Consistent with our results, it is well documented that endurance-trained athletes have larger LA size than non-athletes or sedentary controls [12,14,16], and that LV diastolic [21-23,26] and systolic function [13,17,23] are preserved in athletes with LA enlargement. Similarly, Letnes and colleagues observed no association between LA enlargement and reduced LV diastolic function in a healthy adult and elderly population [25].

Moreover, a dose-response relationship between cumulative lifetime training hours and magnitude of LA remodelling has been well-documented in athletes [22,186-188]. In the general adult and elderly population, dose-response associations between level of PA and LA volume [25,189] or LA diameter [190], and between cardiorespiratory fitness and LA volume [25,191] have been demonstrated. Thus, the broad consistency in the literature strengthens the likelihood of a causal relationship between PA and LA remodelling.

Consistent with our results, several meta-analyses have documented that moderate doses of habitual PA reduced the risk of AF [83-86]. Also, the J- or U-shaped dose-response relationship between PA and AF risk is consistent with other studies [85,93-95]. However, as most studies have been performed on males, few studies have explored the association between exercise and AF risk in females only, and the interplay between sex and AF risk with exercise is less well understood [192].

Elliot and colleagues confirmed the classic J-shaped dose-response relationship among males, whereas the authors observed no higher risk of AF among females [193]. Also, Garnvik and colleagues observed the J-shaped association between estimated cardiorespiratory fitness and risk of AF among males, but not among females [170]. Consistent with these findings, a recent meta-analysis also confirmed the J-shaped association in males, whereas risk of AF remained

lowered among females [86]. Similarly, in a meta-analysis by Zhu and colleagues, the authors reported that intensive PA decreased the AF risk among females, but tended to increase the risk among males [194]. These observations have also been shown in a study of 210000 Swedish skiers (40% females), where the authors demonstrated that female skiers had lower AF risk compared with age and sex-matched non-skiers independent of numbers of races or finishing time [195]. However, males had similar AF risk as matched non-skiers, where those with fastest finishing time and number of races had the highest risk [195]. In contrast to these studies, Myrstad and colleagues observed a J-shaped association between years of previous endurance training and AF risk among females [196]. Similarly, Morseth and colleagues observed a J-shaped association between level of PA and AF risk in both males and females [93].

In summary, the broad consistency in the literature strengthens the likelihood of a causal relationship between moderate doses of habitual PA and reduced risk of AF in both sexes. Furthermore, consistency in the literature strengthens the likelihood of a causal relationship between high levels of exercise training and increased risk of AF in males, whereas the literature is still inadequate and inconsistent for females.

6.3 Experiment confirmation

Usually, randomised trials in humans offer the best protection against confounding and bias, and are widely regarded the gold standard in defining causal associations [135]. Moreover, experimental observations should be integrated with epidemiological observations, to confirm that results from controlled experiments also is applicable in free-living populations [136]. Thus, experiment confirmation of our associations will strengthen the likelihood of a causal relationship.

The relationship between high-intensity endurance training and LA enlargement has been confirmed in randomised trials of middle-aged sedentary adults [20] and in endurance-trained males [197]. Furthermore, six weeks of high-intensity endurance training three times weekly increased LAVi by 19% among endurance-trained males [197]. Similarly, ten months of high-intensity endurance training 5–6 hours per week increased LAVi by 18.5% among sedentary adults [20]. Interestingly, LA volumes were substantially smaller when compared with healthy age-matched masters athletes with a long history of endurance training [20]. However, despite experiment confirmation of the relationship between high-intensity endurance training and

LA remodelling, the association between moderate doses of habitual PA and LA remodelling has not been experimentally confirmed.

Experiment confirmation of the association between exercise and risk of incident AF, or exercise-induced LA remodelling and incident AF risk, is to the best of my knowledge absent, partly due to due to practical (e.g., low adherence to prolonged exercise trials, cross-over from control to intervention group) [198], and ethically challenges (subjects cannot be instructed to be inactive for several years). However, in a randomised trial of Norwegian AF patients with non-permanent AF, the authors demonstrated that high-intensity endurance training three times weekly for 12 weeks reduced AF burden (time in AF and severity) [199].

6.4 Temporality

For the association to be causal, the exposure must precede the outcome [136]. However, demonstrating temporality does not usually establish causality, as the association may be explained by change in other exposure factors (e.g., risk factors) [136]. In contrast, failing to demonstrate an association between an exposure preceding an outcome, is the only viewpoint that may eliminate the possibility of a causal relationship [135,136].

Due to the design of the studies constituting this thesis, judgment of temporality between exposure and outcome was only possible for paper III. At baseline in paper III, we excluded all participants with known cardiac pathology, including AF, and the participants were divided into groups based on LA size (normal/enlarged) or activity level (inactive/active). Thereafter, the participants were followed from the date of examination at baseline, until a) date of first documented AF, b) date of censoring due to death or migration, or c) end of follow-up, whichever came first. Temporality was confirmed for the joint associations of PA and LA size risk of incident AF, for both sexes and age groups.

6.5 Biological plausibility

Biological plausibility strengthens the case for a causal relationship between exposure and outcome [136]. However, for truly novel observations, biological plausibility may not be evident due to limitations in current biological knowledge [136].

The association between PA and LA remodelling may be explained by the hemodynamic pressure and volume overload during exercise, which represents the key stimulus for exercise-induced cardiac remodelling [9,200]. Atrial stretch during exercise leads to release of factors from cardiac cells (e.g., insulin-like growth factor 1), which likely induce myocyte growth [30]. High volumes of endurance training expose the left atrium for prolonged atrial stretch, which supports the dose-response relationship we observed between higher levels of habitual PA and LA size. Moreover, according to Laplace's Law, it is biologically plausible that PA induces sufficient stretch stimuli for LA remodelling. As the LA walls are very thin [173], lower levels of exercise volume, or intensity, are necessary to cause atrial stretch stimuli.

The reduced risk of AF with moderate doses of PA may partially be explained by the beneficial effect of PA on modifiable risk factors (Table 1) [87,97]. The main risk factors for AF are high body mass index and hypertension [60,61], and regular exercise is associated with reduced abdominal and visceral fat [201-203], lowered blood pressure [122,204], risk of type 2 diabetes [205], and improved glycemic control [206,207]. In addition, regular exercise may lower systemic inflammation [97,105], which may protect against adverse LA remodelling and reduce the risk of incident AF.

7 Conclusions, implications, and future research

7.1 Conclusions

This thesis aimed to study the association between PA and the structure and function of the left side of the heart in a general adult and elderly population. Moreover, we explored whether exercise-related LA remodelling was associated with adverse cardiac alterations and increased risk of incident AF.

The main conclusions are as follows:

1) Higher levels of cumulative self-reported PA were associated with increased LA diameter in males and participants <65 years, and in females also increased LV diameter and mass. No change in LV diastolic or systolic function, or atrioventricular ratio at rest was observed with higher levels of PA.
2) Higher levels of accelerometry-measured PA were associated with larger LA volume in participants <70 years with normal LV diastolic function. LA enlargement was associated with indices of LV diastolic dysfunction in the least active quartile of individuals only.
3) Moderate levels of habitual self-reported PA were associated with reduced risk of AF, and LA enlargement was associated with higher risk of AF. However, active individuals with LA enlargement did not have higher risk of AF than neither active nor inactive with normal LA size. Inactive with LA enlargement had considerably higher risk of AF than all other groups.

7.2 Implications for public health

This thesis provides knowledge about the relationship between moderate doses of PA and cardiac adaptations in the general adult and elderly population. Previously, this knowledge has been based mainly on athletes. Device-measured PA facilitates more objective and nuanced understanding of how PA relates to cardiac remodelling, and contributes to increased understanding of how the lower part of the exercise-spectrum associates with cardiac remodelling.

We observed that moderate doses of habitual PA were associated with reduced risk of incident AF, also among subjects with LA enlargement. Importantly, less than one hour of weekly MVPA was sufficient to be associated with reduced risk of incident AF with 60% among those with LA enlargement. Increased knowledge about the beneficial relationship between PA and AF may guide clinicians in implementing PA for primary and secondary prevention of AF. Moreover, prevalence of AF includes 43.6 million individuals worldwide [50], and largely due to increased longevity in the general population, a 2.3-fold increase in AF is expected in the coming decades [50]. Thus, prevention of AF could reduce the burden on healthcare systems considerably.

Moreover, we observed that moderate levels of habitual PA were associated with LA remodelling, and that exercise-induced cardiac remodelling is not a physiological phenomenon only applicable to endurance athletes. Despite LA remodelling, no changes in LV pump function or atrioventricular ratio at rest were observed with higher levels of PA. Importantly, among those with LA enlargement, only the most inactive subjects (~11 min moderate PA/day, data not shown) were related to reduced LV diastolic function. Such knowledge about the relationship between PA and cardiac remodelling may help physicians distinguish between physiological- and pathological remodelling.

7.3 Future research

In order to cover existing knowledge gaps in the association between PA and cardiac remodelling, longitudinal studies should explore the relationship between different levels of device-measured PA and changes in cardiac structure and function evaluated by use of current recommended and novel echocardiographic measurements (e.g., biplane-derived volumes, tissue Doppler, and LA and LV strain). These analyses are most likely possible to perform

when the data collection for the upcoming Tromsø8 (planned to be conducted in 2025) is completed.

As the knowledge about the association between PA and AF risk is mainly based on self-reports, the association between different levels of device-measured PA and risk of incident AF should be explored. Moreover, the lower threshold to prevent incident AF is an important knowledge gap to elucidate. Accelerometry-measured PA was collected in Tromsø7 (2015-16), and with sufficient time and endpoints, we can explore the association between accelerometry-measured PA and AF risk.

Moreover, prospective studies are warranted to clarify the association between exercise-induced LA enlargement and risk of incident AF, preferably assessed with biplane-derived LA volume and device-measured PA. By including a large sample of very vigorous participants (e.g., athletes) of both sexes, analysis of very vigorous PA in the association between LA enlargement and incident AF is possible.

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Paper I

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Longitudinal Associations Between Cumulative Physical Activity and Change in Structure and Function of the Left Side of the Heart: The Tromsø Study 2007–2016

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Background: Current knowledge about the relationship between physical activity (PA) and cardiac remodeling is mainly derived from cross-sectional studies of athletes, and there is a knowledge gap of this association in the general adult and elderly population. Therefore, we aimed to explore the longitudinal association between cumulative PA and change in cardiac structure and function in a general adult and elderly population.

Methods: This longitudinal study includes 594 participants from the sixth (Tromsø6, 2007–08) and seventh (Tromsø7, 2015–16) survey of the Tromsø Study. Cardiac structure and function were assessed by echocardiography at two time points, and PA was self-reported by questionnaire at both time points. PA volume was expressed as cumulative PA (Low, Moderate, and Hard) and the association with left atrial (LA) and left ventricular (LV) structure and function was assessed using ANCOVA.

Results: Overall, LA diameter index (LADi) increased significantly more in Hard compared to Moderate PA (+0.08 cm/m^2, 95% CI 0.01–0.15, $p = 0.020$) from Tromsø6 to Tromsø7. When stratified by sex or age, higher levels of cumulative PA were associated with increased LADi in males and in participants <65 years only. Indexed LV mass (LVMi) increased significantly more in Moderate than in Low PA (+3.9 g/m$^{2.7}$, 95% CI 0.23–7.57, $p = 0.037$). When stratified by sex or age, these changes in LVMi and indexed LV diameter (LVDi) were only significant in females. No significant associations were observed between cumulative PA and change in relative wall thickness, E/e' ratio, e' velocity, LV ejection fraction, and LADi/LVDi ratio.

Conclusion: Higher levels of cumulative PA were associated with increased LADi in males and participants <65 years, and with increased LVMi and LVDi in females. Despite cardiac chamber enlargement, the pump function of the heart did not change with higher levels of PA, and the atrioventricular ratio was unchanged. Our results indicate that cardiac chamber enlargement is a physiological response to PA.

Keywords: athlete's heart, cardiac, echocardiography, ejection fraction, exercise, left atrium, left ventricle, public health

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INTRODUCTION

Changes in cardiac structure and function can occur as a result of physiological remodeling from exercise or pathological remodeling (1). Whereas, physiological remodeling is considered benign adaptations, pathological remodeling is associated with increased risk of cardiovascular diseases and mortality. Both left atrial (LA) enlargement and left ventricular (LV) hypertrophy are independent risk factors for cardiovascular morbidity and mortality (2–4) in the general population, and occurs in response to risk factors such as hypertension, diabetes mellitus, and obesity via mechanisms such as increased pressure and volume overload (5).

Exercise-induced cardiac remodeling is generally considered a benign physiological adaption of exercise, and is characterized by enlarged cardiac chambers and increased LV wall thickness (6). Paradoxically, exercise-induced cardiac remodeling may mimic pathological remodeling (7, 8), and elite endurance athletes may have cardiac chamber size that overlap the size seen in cardiac pathology (7, 9, 10). However, it is observed that LA function (11, 12) and LV diastolic function (13, 14) are preserved in dynamic sport-elite athletes with LA enlargement, as well as in athletes with LV enlargement (7, 15).

Current knowledge about the relationship between physical activity (PA) and cardiac remodeling is mainly derived from cross-sectional studies of athletes (16), and there is a knowledge gap of this association in the general adult and elderly population. Hence, as most studies investigating the relationship between exercise and cardiac remodeling are cross-sectional, more longitudinal studies are needed. Therefore, our main objective was to explore the longitudinal association between cumulative PA and change in cardiac structure and function in a general adult and elderly population.

MATERIALS AND METHODS

Study Population

The Tromsø Study is a single-center population-based cohort study with seven repeated health surveys of the population of the Tromsø municipality, Norway (17). This study includes participants from the sixth (Tromsø6, 2007–08) and seventh (Tromsø7, 2015–16) survey of the Tromsø Study.

In total, 623 participants provided valid data on self-reported PA in combination with valid echocardiography data from Tromsø6 and Tromsø7. We excluded participants with valvular heart disease at baseline ($n = 21$). Furthermore, eight participants were excluded due to missing data on the covariate hypertension. Finally, our analytical sample consisted of 594 participants free from valvular heart disease, and with valid data on PA, echocardiography, and covariates at baseline (**Figure 1**). However, the number of participants differed slightly between the different analyses due to missing images and/or due to images with inappropriate quality.

Physical Activity

PA was assessed using the Saltin-Grimby Physical Activity Level Scale (18), where the participants rank their leisure-time PA on a four-level scale. In our study, we summed up the participants' ranked leisure-time PA in Tromsø6 and Tromsø7 and combined them in a total cumulative score (**Figure 2**). Furthermore, we divided the cumulative score into three cumulative PA categories: (1) Low (total score 2–3), (2) Moderate (total score 4), and (3) Hard PA (total score 5-8).

Cardiac Structure and Function

Echocardiographic examinations in Tromsø6 and Tromsø7 were performed by two qualified sonographers, for Tromsø6 collected from October 2007 to December 2008, using an Acuson Sequoia C512 (Acuson, Mountain View, California, USA) ultrasound scanner and for Tromsø 7 collected from August 2015 to October 2016 using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. The echocardiographic assessments were performed with the use of standard imaging planes in the left lateral decubitus position according to the joint American and European guidelines (19). In Tromsø6, the echocardiographic measurements were performed online in one heart cycle but remeasured if deviating from eye-balled estimates. In Tromsø7, the echocardiographic measurements were performed off-line on 3–5 consecutive cardiac cycles by a physician experienced in echocardiography (co-author MS), and the average was used in the analysis.

Cardiac dimensions were measured by M-mode echocardiography in the parasternal short axis view at the aortic valve level, after alignment of left ventricle in long axis view, according to the leading edge-to-leading edge convention (19). LV internal dimensions were measured at the end of diastole and systole and indexed to body surface area (LVDi) as cm/m^2 (20). LA anteroposterior diameter was measured at the end of the LV systole and indexed to body surface area (LADi) as cm/m^2. LA volume was measured at the end of the LV systole and calculated using the Simpson's biplane method from the apical four- and two chamber views and indexed to body surface area as mL/m^2. LADi/LVDi ratio was calculated. Relative wall thickness was calculated with the formula (2 x posterior wall thickness) / (LV internal end-diastolic diameter). LV myocardial mass was calculated according to the cube formula (19), and further indexed to height by raising height to the power of 2.7 (LVMi), and are presented as $g/m^{2.7}$ (21). LV ejection fraction (LV EF) was calculated using the Teichholz formula (22).

All Doppler examinations were performed in apical four-chamber view according to current recommendations (23). Mitral valve Doppler measurements were performed with a 2 mm Doppler sample volume placed between the mitral leaflet tips. Tissue Doppler measurements were performed with a 5 mm Doppler sample volume located at the septal and lateral side of the mitral annulus. Measurement of peak flow velocity in early diastole (E-wave) was measured with pulsed Doppler. Mitral annular e' velocity was measured with pulsed-wave tissue Doppler in both lateral and septal basal regions and furthermore averaged. E/e'ratio was calculated. Valvular heart disease was defined by the following criteria: (a) aortic stenosis

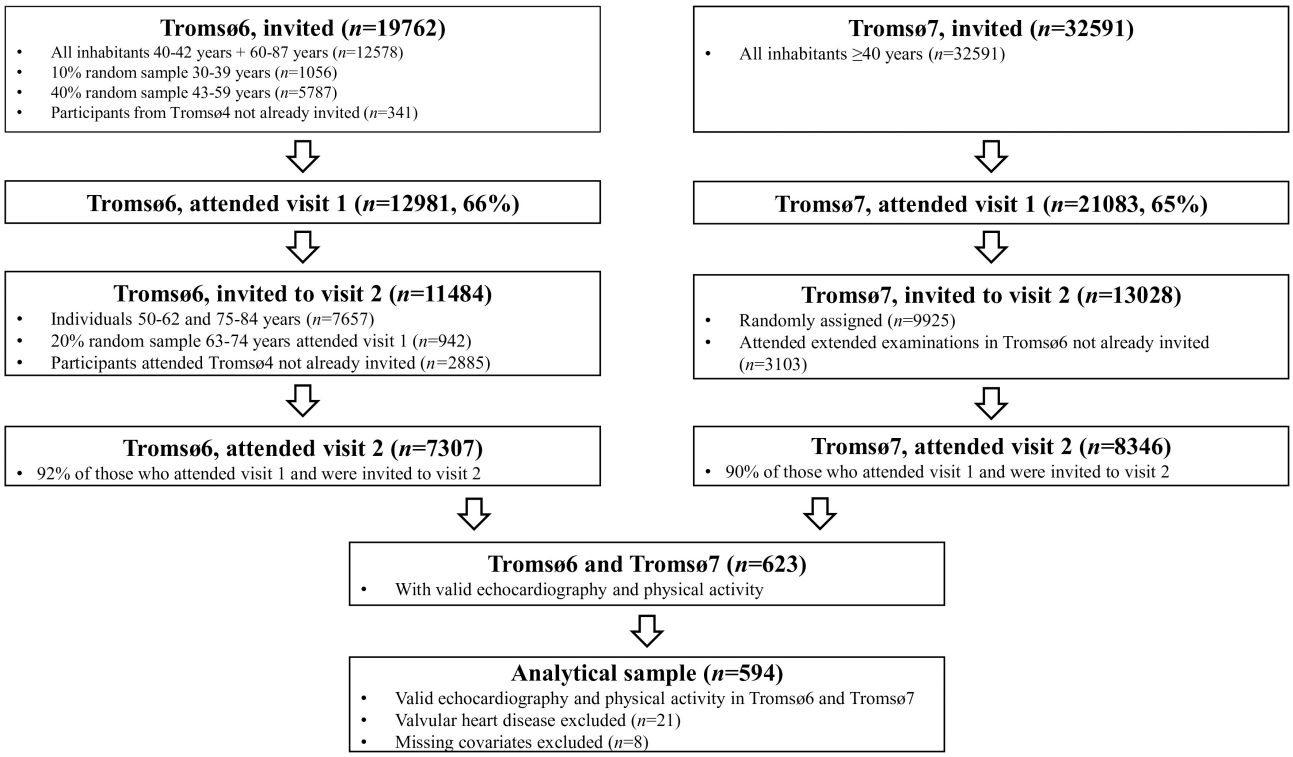

FIGURE 1 | Flowchart over inclusion of participants: The Tromsø Study 2007–2016.

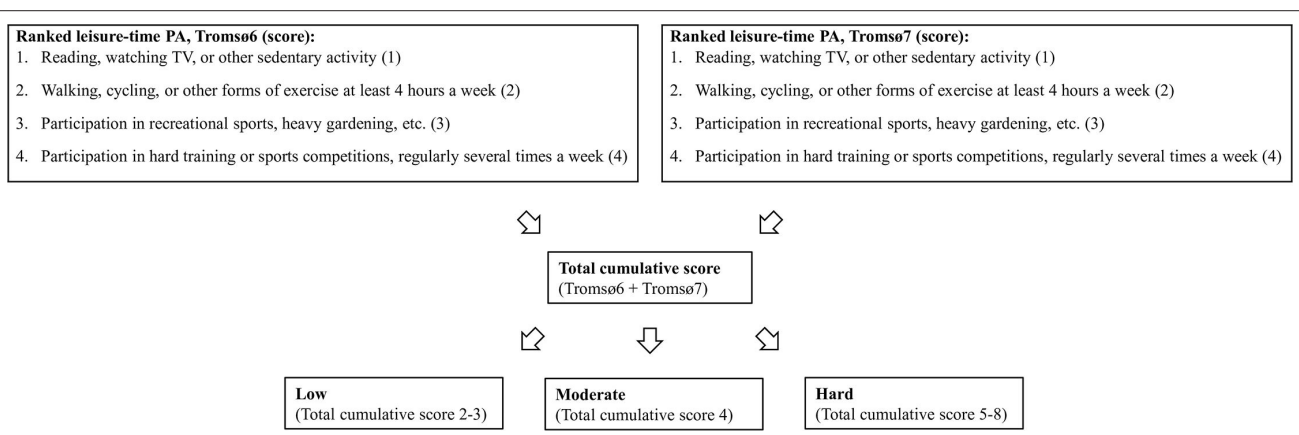

FIGURE 2 | Overview of summation of PA from Tromsø6 and Tromsø7 into cumulative PA categories: The Tromsø Study 2007–2016. PA: physical activity.

(aortic valve mean gradient ≥15 mmHg) by continuous Doppler (24), (b) presence of mitral or (c) aortic regurgitation detected by color Doppler imaging with mitral insufficiency graded according to regurgitant jet area >4 cm^2 (25), and aortic regurgitation graded by vena contracta width by color M-mode divided by of LV outflow tract diameter (>30% graded as moderate or higher) (25), and/or (d) mitral stenosis (E-wave deceleration time >350 msec and mitral E-wave >1 m/s) by pulsed Doppler (26). However, mitral stenosis was not identified in any subjects in our analytical sample.

In Tromsø7, an intra- and inter-observer study was performed on the echocardiography data (27). Intra-class correlation coefficients on Doppler indices and linear measurements were 0.90–0.99 in the intra-observer study and 0.84–0.98 in the inter-observer study. In Tromsø6, intra- and inter-observer variability on Doppler indices was evaluated by Bland-Altman analysis (24). The results showed mean inter-observer differences (95% limits

of agreement) in the mean aortic gradient of −0.06 mmHg (−3.06 to 3.18). Intra-observer analysis gave a mean difference of −0.04 mmHg (−1.86 to 1.78) and 0.30 mm Hg (−3.96 to 4.56), respectively, in the two observers.

Covariates

Details about collection of baseline data are described elsewhere, and all data were collected by specially trained research technicians (28). Baseline data from Tromsø6 include the following covariates extracted from self-reported questionnaires, physical examinations, and blood samples: Daily smoking (yes or previously/never), diabetes (yes/no), use of antihypertensives (currently or previously/never), myocardial infarction (previously/no), stroke (previously/no). Alcohol consumption was the product of two questions, one reporting number of units of alcohol and one reporting frequency of drinking.

Blood pressure was recorded three times with 1 min intervals after 2 min seated rest with an automatic device (Dinamap Pro care 300 Monitor, GE Healthcare, Oslo, Norway), the average from reading two and three was used in our analyses. Blood pressure was classified into hypertension groups (21): (a) Normotensive (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and no self-reported use of antihypertensives), (b) hypertensive, controlled (systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, and self-reported use of antihypertensives), (c) hypertensive, uncontrolled (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and self-reported use of antihypertensives), or d) hypertension, untreated (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and no self-reported use of antihypertensives). Height and weight were measured to the nearest decimal with participants wearing light clothing and no footwear. Body mass index was calculated as weight (kg) divided by height squared (m^2).

Data on atrial fibrillation was derived from the diagnosis registry of the University Hospital of North Norway, the only hospital in the region, by linking the hospitals records of atrial fibrillation to the participants' unique Norwegian national 11-digit identification number (29). Blood samples were analyzed for low-density lipoprotein (LDL) cholesterol at the Department of Clinical Chemistry, University Hospital of North Norway.

Statistical Methods

Descriptive characteristics of the study population are presented as means with standard deviations (SD) or percentages with number of observations (*n*). The associations between cumulative PA and cardiac structure and function were evaluated by one-way analysis of covariance with Bonferroni adjusted *post hoc* comparisons. Data are presented as adjusted means with standard error (SE), and effects with 95% confidence intervals (CI) unless otherwise stated. Model 1 is unadjusted, model 2 is adjusted for age, sex, body mass index, and hypertension groups.

Sex*PA was a significant interaction term in the association between PA and change in LA diameter (p = 0.024), body mass index*PA was a significant interaction term between PA and change in E/e' ratio (p = 0.028), and hypertension (normotensive/hypertensive)*PA was a significant interaction term between PA and change in average e' ($p = 0.040$).

To test the robustness of the fully adjusted model 2, we performed sensitivity analyses excluding participants with known cardiac pathologies (atrial fibrillation, myocardial infarction, stroke, and LV EF <40%) stepwise. Moreover, we performed sensitivity analysis adjusted for additional covariates (smoking, alcohol consumption, diabetes, and LDL cholesterol) stepwise added to the model.

For sensitivity analyses of the PA assessments, we compared the mean PA score in Tromsø6 with the mean PA score in Tromsø7, stratified by level of cumulative PA (**Supplementary Table S1**), to assess whether there were differences in PA score between Tromsø6 and Tromsø7 within each level of cumulative PA. Moreover, the activity level within each level of cumulative PA was quantified with accelerometry-measured PA, assessed by a triaxial accelerometer (wGT3X-BT, ActiGraph LLC, Pensacola, FL, USA), in Tromsø7 (**Supplementary Table S2**).

All statistical analyses were performed using SPSS version 28 (SPSS Inc., IL, USA), with a two-sided alpha ≤0.05 considered statistically significant.

RESULTS

In total, 266 males (61.1 ± 8.9 years) and 328 females (58.9 ± 9.9 years), ranging from 37 to 76 years, were included in our study. Descriptive baseline characteristics of the analytical sample, stratified by PA, is given in **Table 1**.

Overall, there was a significant difference in increase in LADi ($p = 0.018$) and LVMi ($p = 0.037$) between groups of cumulative PA in multivariate adjusted analyses (**Supplementary Table S3**). No significant differences were observed between cumulative PA and change in the other echocardiography variables (LVDi, relative wall thickness, E/e' ratio, e' velocity, LV EF, and LA/LV ratio) (**Supplementary Table S3**).

Cumulative PA and Change in LADi From Tromsø6 to Tromsø7

Overall, from Tromsø6 to Tromsø7, LADi increased significantly more in Hard compared to Moderate PA, with a mean group difference in LADi enlargement of 0.08 cm/m^2 (95% CI 0.01–0.15, p = 0.020) (**Table 2**). No significant differences in LADi change were observed between Hard and Low PA ($p = 0.128$) and Moderate and Low PA ($p = 1.000$).

In sex-stratified adjusted analysis (**Table 2**), LADi in males increased significantly more in Hard (0.30 cm/m^2, SE 0.03) than in Moderate (0.14 cm/m^2, SE 0.03) and Low PA (0.18 cm/m^2, SE 0.04), with a mean group difference of 0.12 cm/m^2 (95% CI 0.00–0.24, p = 0.047) between Hard and Low, and a mean group difference of 0.16 cm/m^2 (95% CI 0.06–0.26, $p < 0.001$) between Hard and Moderate PA. No statistical difference between Moderate and Low PA was observed ($p = 1.000$). In females, no differences were observed ($p = 0.852$).

TABLE 1 | Descriptive baseline characteristics stratified by level of cumulative physical activity: The Tromsø Study 2007–2008.

	Low PA ($n = 140$)	Moderate PA ($n = 259$)	Hard PA ($n = 195$)	Total ($n = 594$)
Age, years	61.4 (9.0)	59.2 (9.4)	59.9 (10.0)	60.0 (9.6)
Sex, % (*n*) female	60.7 (85)	62.9 (163)	41.0 (80)	55.2 (328)
Body mass index kg/m^2	28.1 (4.6)	26.3 (3.7)	26.3 (3.6)	26.7 (4.0)
Systolic blood pressure, mmHg	141.1 (21.0)	136.6 (20.9)	136.6 (22.7)	137.7 (21.6)
Diastolic blood pressure, mmHg	78.1 (10.7)	78.0 (9.7)	78.4 (10.5)	78.2 (10.2)
LDL cholesterol, mmol/L	3.7 (1.0)	3.6 (1.1)	3.6 (0.9)	3.6 (1.0)
Hypertension, controlled, % (*n*)	11.4 (16)	6.2 (16)	6.2 (12)	7.4 (44)
Hypertension, uncontrolled, % (*n*)	17.9 (25)	11.6 (30)	15.4 (30)	14.3 (85)
Hypertension, untreated, % (*n*)	32.1 (45)	34.7 (90)	29.7 (58)	32.5 (193)
Myocardial infarction, %	5.8 (8)	5.0 (13)	3.7 (7)	4.8 (28)
Stroke, %	2.9 (4)	1.2 (3)	2.1 (4)	1.9 (11)
Atrial fibrillation, %	2.9 (4)	1.2 (3)	2.6 (5)	2.0 (12)
Diabetes, %	8.7 (12)	2.7 (7)	3.7 (7)	4.4 (26)
Smoking daily, % (*n*)	23.9 (33)	18.1 (47)	8.8 (17)	16.4 (97)
Alcohol, units/month	9.8 (13.6)	9.6 (11.1)	10.8 (11.6)	10.1 (11.9)
Echocardiography				
LV mass, g	176.5 (54.9)	155.1 (44.9)	175.2 (55.4)	166.7 (51.9)
LV mass, g female	156.3 (40.5)	132.2 (28.7)	138.8 (33.7)	139.9 (34.6)
LV mass, g male	207.3 (59.9)	194.0 (40.4)	200.8 (53.5)	199.7 (50.7)
LV mass index, g/h$^{2.7}$	42.8 (12.2)	37.5 (8.7)	40.9 (11.5)	39.8 (10.8)
LV mass index, g/h$^{2.7}$ female	41.6 (12.0)	35.2 (7.7)	36.7 (9.9)	37.2 (9.8)
LV mass index, g/h$^{2.7}$ male	44.5 (12.4)	41.3 (9.0)	43.8 (11.7)	43.1 (11.0)
LA diameter, cm	3.8 (0.5)	3.6 (0.5)	3.8 (0.5)	3.7 (0.5)
LA diameter, cm female	3.6 (0.5)	3.4 (0.4)	3.6 (0.4)	3.5 (0.4)
LA diameter, cm male	4.0 (0.4)	4.0 (0.5)	4.0 (0.6)	4.0 (0.5)
LA diameter index, cm/m^2	2.0 (0.2)	2.0 (0.2)	2.0 (0.3)	2.0 (0.2)
LA diameter index, cm/m^2 female	2.0 (0.3)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
LA diameter index, cm/m^2 male	2.0 (0.2)	2.0 (0.2)	2.0 (0.3)	2.0 (0.3)
LV diameter, cm	5.1 (0.5)	5.0 (0.5)	5.2 (0.5)	5.1 (0.5)
LV diameter, cm female	5.0 (0.5)	4.9 (0.4)	4.9 (0.4)	4.9 (0.4)
LV diameter, cm male	5.3 (0.5)	5.3 (0.5)	5.4 (0.5)	5.3 (0.5)
LV diameter index, cm/m^2	2.7 (0.3)	2.7 (0.3)	2.8 (0.2)	2.7 (0.3)
LV diameter index, cm/m^2 female	2.8 (0.3)	2.8 (0.3)	2.8 (0.2)	2.8 (0.3)
LV diameter index, cm/m^2 male	2.6 (0.2)	2.6 (0.3)	2.7 (0.3)	2.6 (0.3)
LA/LV ratio	0.7 (1.0)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
E/e' ratio	6.6 (1.7)	6.3 (1.4)	6.3 (1.7)	6.3 (1.6)
LV ejection fraction, %	70.8 (7.2)	70.8 (7.2)	71.2 (7.2)	70.9 (7.2)
LV ejection fraction <40%, % (*n*)	0.0 (0)	0.0 (0)	0.6 (1)	0.2 (1)

Numbers are mean ±standard deviation or percentage and n. PA, physical activity, LDL, low-density lipoprotein, LV, left ventricular, LA, left atrial.

In age-stratified adjusted analysis (**Table 2**), LADi in participants <65 years increased significantly more in Hard (0.21 cm/m2, SE 0.03) than in Moderate (0.11 cm/m^2, SE 0.03) PA, with a mean group difference of 0.10 cm/m^2 (95% CI 0.01–0.18, $p = 0.025$). No statistical difference between Hard and Low PA ($p = 0.474$), or between Moderate and Low PA ($p = 1.000$) was observed. No statistical differences in LADi between groups were observed for participants ≥65 years ($p = 0.262$).

Associations between cumulative PA and cross-sectional LADi in Tromsø7 are presented in **Figure 3**. Significant associations between cumulative PA and LADi were observed in males, in participants <65 years, and in the overall analysis. Moreover, similar trends in the association between cumulative PA and LADi were observed in unadjusted, baseline adjusted, and in fully adjusted analysis. Associations between cumulative PA and cross-sectional LA volume index in Tromsø7 are presented in **Figure 4**. Significant associations between cumulative PA and LA volume index were observed in females, in participants <65 years, and in the overall analysis. Moreover, similar trends in the association between cumulative PA and LA volume index were observed in unadjusted, baseline adjusted, and in fully adjusted analysis.

TABLE 2 | Longitudinal associations between cumulative physical activity and change in left atrial diameter index: The Tromsø Study 2007–2016.

	(*n*)	Model 1, baseline (mean ± SE)	Model 1, change (Delta ± 95% CI)	Model 1 (*p*-value)	Model 2, baseline (Adjusted mean ± SE)	Model 2, change (Delta ± 95% CI)	Model 2 (*p*-value)
Total	572			0.011*			0.018*
Low PA	133	1.98 (0.02)	0.19 (0.14, 0.24)	Ref.	2.00 (0.02)	0.18 (0.13, 0.24)	Ref.
Moderate PA	249	1.98 (0.02)	0.17 (0.13, 0.21)	1.000	2.01 (0.02)	0.17 (0.13, 0.22)	1.000
Hard PA	190	2.02 (0.02)	0.26 (0.21, 0.30)	0.139	2.06 (0.02)	0.26 (0.21, 0.30)	0.128
Hard vs. Moderate				0.010			0.020
Males	258			<0.001*			<0.001*
Low PA	54	1.94 (0.04)	0.20 (0.12, 0.28)	Ref.	1.96 (0.04)	0.18 (0.10, 0.27)	Ref.
Moderate PA	91	1.97 (0.03)	0.13 (0.07, 0.19)	0.529	2.00 (0.03)	0.14 (0.08, 0.21)	1.000
Hard PA	113	2.00 (0.02)	0.30 (0.25, 0.35)	0.117	2.02 (0.03)	0.30 (0.24, 0.36)	0.047
Hard vs. Moderate				<0.001			<0.001
Females	314			0.950*			0.852*
Low PA	79	2.01 (0.03)	0.18 (0.11, 0.25)	Ref.	2.03 (0.03)	0.18 (0.10, 0.25)	Ref.
Moderate PA	158	1.99 (0.02)	0.19 (0.14, 0.24)	1.000	2.03 (0.02)	0.20 (0.14, 0.26)	1.000
Hard PA	77	2.05 (0.03)	0.19 (0.12, 0.26)	1.000	2.10 (0.03)	0.21 (0.13, 0.28)	1.000
Hard vs. Moderate				1.000			1.000
<65 years	363			0.015*			0.031*
Low PA	80	1.93 (0.03)	0.17 (0.11, 0.24)	Ref.	1.95 (0.03)	0.15 (0.08, 0.22)	Ref.
Moderate PA	169	1.98 (0.02)	0.13 (0.09, 0.18)	1.000	2.00 (0.02)	0.11 (0.06, 0.17)	1.000
Hard PA	114	1.98 (0.02)	0.24 (0.18, 0.29)	0.388	2.02 (0.03)	0.21 (0.15, 0.27)	0.474
Hard vs. Moderate				0.012			0.025
≥65 years	209			0.420*			0.262*
Low PA	53	2.06 (0.04)	0.21 (0.13, 0.30)	Ref.	2.06 (0.04)	0.23 (0.14, 0.32)	Ref.
Moderate PA	80	2.00 (0.03)	0.25 (0.18, 0.32)	1.000	2.00 (0.03)	0.28 (0.20, 0.26)	1.000
Hard PA	76	2.09 (0.03)	0.29 (0.21, 0.36)	0.585	2.10 (0.03)	0.33 (0.24, 0.41)	0.312
Hard vs. Moderate				1.000			1.000

**p-value for main effect. Left atrial diameter index (LADi) and delta are presented as cm/m^2. Model 1, unadjusted; Model 2, age, sex, body mass index, hypertension groups; PA; physical activity; LA, left atrial; SE, standard error; CI, confidence interval.*

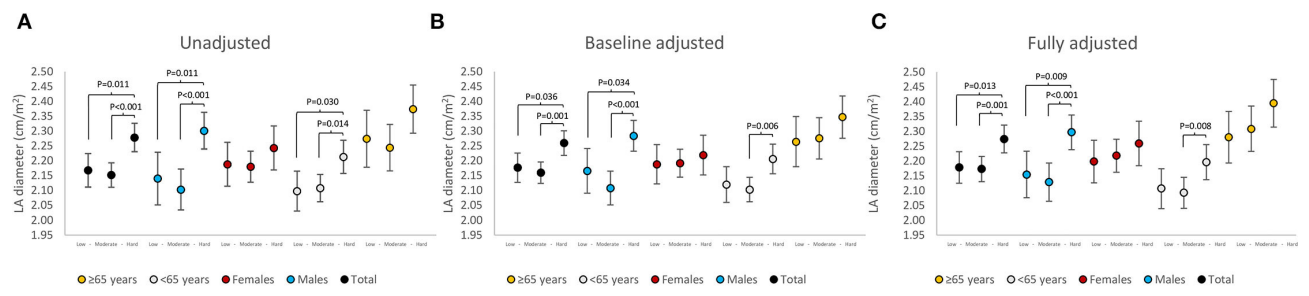

FIGURE 3 | Associations between cumulative PA and cross-sectional LA diameter index (LADi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LADi in Tromsø6, **(C)** is adjusted for baseline LADi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA are indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LA, left atrial; CI, confidence interval.

Cumulative PA and Change in LVMi From Tromsø6 to Tromsø7

Overall, from Tromsø6 to Tromsø7, LVMi increased significantly more in Moderate compared to Low PA, with a mean group difference in LVMi enlargement of 3.9 g/m$^{2.7}$ (95% CI 0.23–7.57, $p = 0.037$) (**Table 3**). No significant differences in LVMi change were observed between Hard and Low PA ($p = 0.172$) and Hard and Moderate PA ($p = 1.000$).

In sex-stratified adjusted analysis (**Table 3**), LVMi in females increased significantly more in Moderate than in Low PA, with a mean difference in change of 5.6 g/m$^{2.7}$ (95% CI 1.61–9.53, $p = 0.002$), and in Moderate than Hard PA, with a mean difference in LVMi enlargement of 4.1 g/m$^{2.7}$ (95% CI 0.35–7.92, $p = 0.027$). No significant difference between Hard and Low PA (p=1.000) was observed. In males, no significant differences were observed ($p = 0.224$). In age-stratified adjusted analysis (**Table 3**), no significant differences were observed ($p \geq 0.182$).

TABLE 3 | Longitudinal associations between cumulative physical activity and change in left ventricular mass index from baseline: The Tromsø Study 2007–2016.

	(*n*)	Model 1, baseline (Mean ± SE)	Model 1, change (Delta ± 95% CI)	Model 1 (*p*-value)	Model 2, baseline (Adjusted mean ± SE)	Model 2, change (Delta ± 95% CI)	Model 2 (*p*-value)
Total	494			0.077*			0.037*
Low PA	109	42.0 (1.0)	2.91 (0.53, 5.30)	Ref.	40.8 (0.9)	2.02 (−0.67, 4.70)	Ref.
Moderate PA	218	37.1 (0.7)	6.29 (4.60, 7.97)	0.071	38.8 (0.7)	5.92 (3.84, 8.00)	0.033
Hard PA	167	40.3 (0.8)	5.28 (3.35, 7.21)	0.391	41.1 (0.8)	5.10 (2.88, 7.33)	0.172
Hard vs. Moderate				1.000			1.000
Males	215			0.335*			0.224*
Low PA	43	45.1 (1.6)	3.46 (−0.93, 7.84)	Ref.	42.4 (1.6)	3.31 (−1.53, 8.15)	Ref.
Moderate PA	78	40.9 (1.2)	3.97 (0.71, 7.23)	1.000	41.7 (1.2)	3.86 (0.04, 7.68)	1.000
Hard PA	94	43.2 (1.1)	6.74 (3.77, 9.70)	0.670	44.3 (1.1)	7.25 (3.79, 10.72)	0.516
Hard vs. Moderate				0.651			0.412
Females	279			0.002*			0.001*§
Low PA	66	40.0 (1.1)	2.56 (−0.08, 5.19)	Ref.	38.9 (1.1)	0.86 (−2.17, 3.89)	Ref.
Moderate PA	140	35.0 (0.8)	7.58 (5.77, 9.39)	0.007	36.4 (0.9)	6.43 (4.09, 8.77)	0.002
Hard PA	73	36.6 (1.1)	3.40 (0.89, 5.91)	1.000	38.3 (1.0)	2.30 (−0.56, 5.15)	1.000
Hard vs. Moderate				0.025			0.027
<65 years	339			0.431*			0.182*§
Low PA	71	40.3 (1.1)	4.91 (2.44, 7.38)	Ref.	40.4 (1.1)	3.56 (0.67, 6.46)	Ref.
Moderate PA	158	36.2 (0.7)	6.84 (5.19, 8.50)	0.604	38.5 (0.8)	6.39 (4.23, 8.56)	0.196
Hard PA	110	37.3 (0.9)	5.97 (3.99, 7.96)	1.000	39.0 (0.9)	5.67 (3.34, 8.00)	0.616
Hard vs. Moderate				1.000			1.000
≥65 years	155			0.223*			0.204*
Low PA	38	45.1 (1.8)	−0.81 (−6.02, 4.40)	Ref.	42.9 (1.7)	−0.66 (−6.31, 4.99)	Ref.
Moderate PA	60	39.5 (1.5)	4.83 (0.68, 8.98)	0.289	40.0 (1.5)	5.20 (0.60, 10.44)	0.255
Hard PA	57	46.2 (1.5)	3.94 (−0.31, 8.20)	0.494	45.9 (1.6)	4.71 (−0.51, 9.93)	0.459
Hard vs. Moderate				1.000			1.000

**p-value for main effect.*

§Assumption of equality of error variances is violated.

Left ventricular mass index (LVMi) and delta are presented as g/m$^{2.7}$.

Model 1, unadjusted; Model 2, age, sex, body mass index, hypertension groups; PA, physical activity; LV, left ventricular; SE, standard error; CI, confidence interval.

In analysis of the association between cumulative PA and change in LVDi, significant associations were observed in females only (**Supplementary Table S4**). LVDi increased significant more in Moderate (0.07 cm/m^2 ± SE 0.03) than in Low PA (−0.06 cm/m^2, SE 0.04), with a mean group difference of 0.13 cm/m^2 (95% CI 0.03 to 0.24, $p = 0.010$). However, no significant differences in LVDi change were observed between Hard and Low PA ($p = 0.087$) and Hard and Moderate PA ($p = 1.000$).

Associations between cumulative PA and cross-sectional LVMi in Tromsø7 are presented in **Figure 5**. Significant associations between cumulative PA and LVDi were observed in females only. Moreover, similar trends in the association between cumulative PA and LVMi were observed in unadjusted, baseline adjusted, and in fully adjusted analysis.

Cumulative PA and Change in Cardiac Function From Tromsø6 to Tromsø7

The observed association observed between cumulative PA and change in LA/LV ratio overall ($p = 0.075$), stratified by sex ($p \geq 0.065$), or stratified by age ($p \geq 0.083$) was non-significant (**Supplementary Table S5**). No significant association was observed between cumulative PA and change in Mitral annular e' velocity overall ($p = 0.903$), stratified by sex ($p \geq 0.529$), stratified by age ($p \geq 0.749$), or stratified by hypertension ($p \geq 0.196$) (**Supplementary Table S6**). No significant association was observed between cumulative PA and change in change in E/e' ratio overall ($p = 0.253$), stratified by sex ($p \geq 0.286$), stratified by age ($p \geq 0.213$), or stratified by body mass index ($p \geq 0.180$) (**Supplementary Table S7**). No significant association was observed between cumulative PA and change in LV EF overall ($p = 0.970$), stratified by sex ($p \geq 0.652$), or stratified by age ($p \geq 0.556$) (**Supplementary Table S8**).

Sensitivity Analysis

When we stepwise, or jointly, excluded participants with known cardiac pathologies, we observed rather similar associations between cumulative PA and change in echocardiography measurements as in the fully adjusted

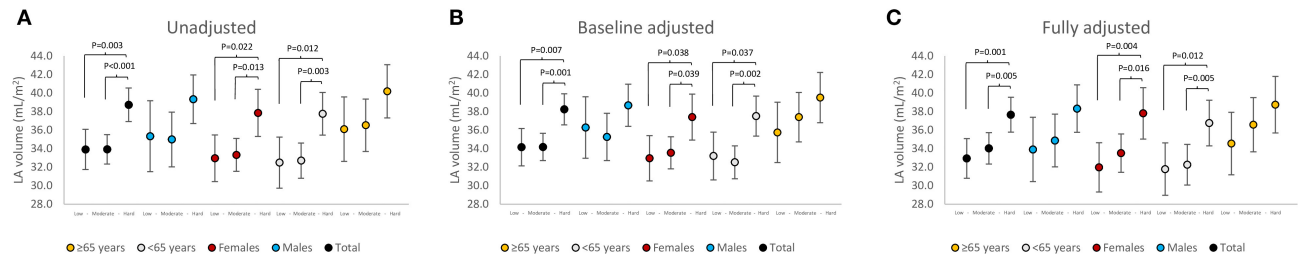

FIGURE 4 | Associations between cumulative PA and cross-sectional LA volume index (LAVi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LADi in Tromsø6, **(C)** is adjusted for baseline LADi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA is indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LA, left atrial; CI, confidence interval; LADi, LA diameter index.

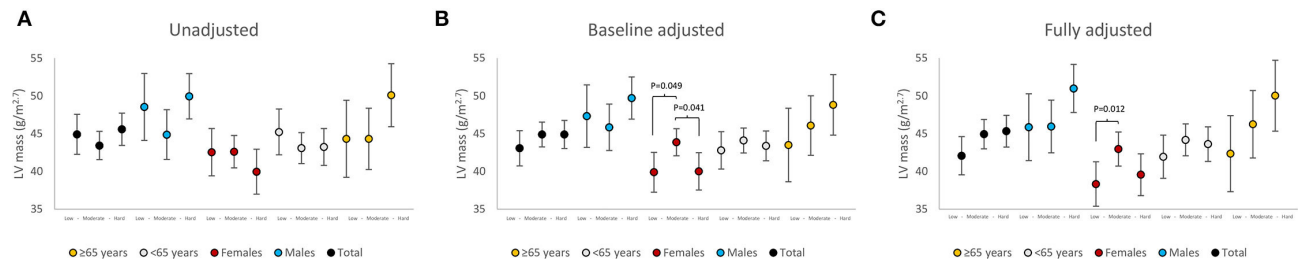

FIGURE 5 | Associations between cumulative PA and cross-sectional LV mass index (LVMi) in Tromsø7. **(A)** is unadjusted, **(B)** is adjusted for baseline LVMi in Tromsø6, **(C)** is adjusted for baseline LVMi in addition to age, sex, body mass index, and hypertension groups. Differences between groups of cumulative PA are indicated with *p*-values. Error bars indicate 95% CI. PA, physical activity; LV, left ventricle; CI, confidence interval.

model 2 (**Supplementary Table S9**). Furthermore, when smoking, alcohol consumption, diabetes, and LDL cholesterol were stepwise added to model 2, the associations between cumulative PA and change in LADi and between cumulative PA and change in LVMi did not change, except when diabetes was added to the model, the association between cumulative PA and LVMi was no longer significant ($p = 0.068$).

DISCUSSION

Exercise-induced cardiac remodeling is well documented in athletes. Our longitudinal study adds to this knowledge by showing that more moderate levels of habitual PA over time is associated with cardiac remodeling also in a general adult and elderly population. The main finding from our study is that higher levels of cumulative PA was associated with increased LA size in males and in participants <65 years, and that moderate level of cumulative PA was associated with increased LV size in females.

Despite the association between cumulative PA and increased LA and LV sizes, indices of cardiac pump function and atrioventricular remodeling did not differ significantly between groups of cumulative PA. This may indicate that cardiac chamber enlargement is a physiological response to PA.

Cumulative PA and Increased LA and LV Sizes

In our study of the general population, we observed that Hard cumulative PA was associated with a larger increase in LADi than lower PA levels; although when stratified by sex or age, increased LADi was only observed in males and in participants <65 years. Furthermore, Moderate cumulative PA was associated with increased LVMi and LVDi, but only in females when stratified by sex or age.

Our observations are at large consistent with previous studies of athletes. Several meta-analyses have reported that LA and LV sizes are larger in endurance trained athletes compared to non-athletes or sedentary controls (9, 30–32). Moreover, the relationship between endurance training and increased LV volume and mass has been demonstrated in a recent meta-analysis of both males and females (33). Additionally, the relationship between endurance training and increased LA volume, LV volume and LV mass has been confirmed in endurance trained young male and female athletes after 90 days of training (34). Similarly, increased LV volume and mass has been demonstrated in young sedentary males and females after 1 year of intensive endurance training (35).

Furthermore, the relationship between endurance training and enlarged LA volume and LV volume has been confirmed in middle-aged sedentary males and females after 10 months high-intensity endurance training (36); both LA and LV volumes increased significantly, but were considerably smaller when compared with a control group of age matched endurance athletes with a long history of endurance training (36). Additionally, a relationship between high levels of cumulative lifetime training hours and larger LA volume has been observed in males (37, 38), but no association between cumulative lifetime training hours and change in LV diameter or mass (38). Similarly,

Mahjoub and colleagues demonstrated that LA volume increased after only 6 weeks of high-intensity endurance training in endurance trained men, whereas no change in LV mass, volume, or diameter was seen (39).

The findings from the previously discussed studies demonstrate that extensive LA and LV remodeling requires high amounts of endurance training stimuli over a long time. Similarly, our results indicate that the left atrium adapts faster to exercise than the left ventricle, and that sufficient and potentially higher stimulus from exercise intensity and volume is required for the left ventricle to remodel. The faster LA remodeling may be explained by the fact that the LA walls are thinner than the LV walls (11), and therefore are more affected by the hemodynamic overload during exercise according to the Laplace's law. In our study, the stimulus from moderate levels of habitual PA over time may have been insufficient to induce LV remodeling, which may explain the lack of association between cumulative PA and increased LV sizes in our study, except for females with Moderate PA. Furthermore, the lack of association between cumulative PA and change in LV size is supported by our sensitivity analysis, as the association between cumulative PA and change in LVMi became weaker and non-significant when we adjusted for diabetes.

Age and Sex Modifications

It is well documented that the prevalence of cardiovascular risk factors such as hypertension increase progressively with age, with a prevalence of 60% in participants ≥60 years (21). Untreated hypertension causes LV hypertrophy, which impairs LV relaxation and induces LV diastolic dysfunction and LA enlargement (21). Thus, the lack of increase in LADi in participants ≥65 years may be due to age related changes in the heart.

The observed sex differences in the association between cumulative PA and LA size may be explained by physiological and morphological differences between males and females (40). Females are on average smaller, have lower lean mass and a different sex hormone profile than males, which significantly impacts cardiac size (41). As females generally have smaller cardiac chambers than males (19), males exhibit more pronounced cardiac changes despite similar relative increase in chamber sizes (41). Finally, there may be quantitative and qualitative differences in exercise patterns between males and females (40). This is supported by accelerometry-measured data from the general adult and elderly population, where females accumulated more minutes of light PA and males accumulated more minutes of moderate and vigorous PA (42, 43).

Cumulative PA and Change in Cardiac Function

Despite the association between cumulative PA and increased LA and LV sizes, no significant differences in mitral annular e' velocity, E/e' ratio, LV EF, or LADi/LVDi ratio were observed between groups of cumulative PA. Thus, our results demonstrate that changes in indices of LV diastolic and systolic function, and atrioventricular chamber ratio, do not differ between groups of cumulative PA. The observed cardiac chamber enlargement with higher levels of cumulative PA in our study seems to be a physiological adaptation to exercise.

Our observations are consistent with previous reports of preserved cardiac function in athletes with exercise-induced cardiac remodeling. Studies of endurance athletes and elite soccer players have observed that LV diastolic function, as measured by Mitral valve and/or Tissue Doppler imaging, is preserved or even supranormal in athletes with cardiac chamber enlargement (13, 14, 38, 44). Also, studies have observed that LV systolic function, as measured by LV EF and/or LV fractional shortening, is normal in athletes with cardiac chamber enlargement (13, 15). Furthermore, preserved LV systolic function in athletes, as measured by LV EF and LV fractional shortening, has been confirmed in a meta-analysis of males and females at rest and during exercise (31). The authors observed no differences in LV systolic function between athletes and matched control subjects (31). Additionally, the effects of endurance training has been evaluated in a recent meta-analysis, where it was demonstrated that LV systolic function, as measured by LV EF and LV stroke volume, was slightly increased in males, but unaltered in females (33). In cross-sectional studies from the general population, no significant associations between increased LA volume and LV diastolic dysfunction, as measured by E/e' ratio, e', and/or tricuspid regurgitation velocity, was observed in physically active participants (45, 46).

In contrast, Lakatos and colleagues observed normal, but lower LV systolic function, as measured by LV EF and/or LV global longitudinal strain, in elite endurance athletes compared to non-athletes (47). Similarly, despite no difference in LV EF, it has been observed that LV global longitudinal strain was lower in elite endurance athletes than in non-athletes (13). With exercise-induced LV remodeling, it is possible that less myocardial deformation is required to obtain the same stroke volume. Therefore, reduced LV global longitudinal strain may be an adaptive change in elite endurance athletes (13).

Our observations of a balanced LADi/LVDi ratio, despite increased LA and LV sizes, is consistent with studies observing symmetrical enlargement of all four chambers (34), and that LA volume/LV volume ratio is similar despite LA enlargement in endurance athletes (13). An increased LA/LV ratio may be due to increased LV pressure and/or LV diastolic impairment, whereas an increased LA chamber with normal LA/LV ratio likely reflects a physiological adaptation to exercise (13).

In contrast to preserved pump function and balanced remodeling in the athlete's heart, increased risk of atrial fibrillation is seen in both adult and elderly endurance athletes (48, 49). It is suggested that LA enlargement itself may be a substrate for atrial fibrillation in athletes (50, 51), and therefore that the athlete's heart may potentially be proarrhythmic independent of other abnormalities. However, convincing data linking the combination of exercise and LA size to AF are lacking and are largely speculative (50, 52). Moreover, in a recent study investigating the acute effects of strenuous endurance exercise on atrial size and function in master athletes (53), the authors reported no exercise-induced atrial dysfunction or change in atrial size after an ultramarathon compared with

baseline. Moreover, acute exercise-induced atrial fibrillation was uncommon during the race (53).

Strengths and Limitations

The main strength of our study is the longitudinal design with repeated measurements of PA and echocardiographic structural and functional data, which enables evaluation of the direction of the associations as well as change from baseline. Moreover, the broad diversity of covariates allowed us to adjust for multiple potential confounders.

Our study has several limitations that should be addressed. First, due to the observational nature of this study, causation cannot be established. Second, LADi, LVDi, and LV EF were assessed by linear measurements, which are less accurate and have more geometrically assumptions than the recommended biplane volume calculated parameters (19). However, in Tromsø7, we found moderate correlation between biplane-calculated EF and Teichholz-calculated EF ($r = 0.42$), and between LADi and LA volume index ($r = 0.45$). Furthermore, LVDi correlated strongly with LV volume index ($r = 0.87$). Third, our study lacks assessment of LA function which may distinguish between pathological and physiological remodeling (8). Fourth, self-reported PA is prone to both recall- and social desirability bias (54), and misclassifications would probably underestimate the true effects of PA. However, in a sub-study of Tromsø6, self-reported PA using the Saltin-Grimby Physical Activity Level Scale was significantly correlated with maximal oxygen uptake (females $r_s = 0.40$, males $r_s = 0.44$, both $p < 0.001$) (55). Moreover, there was a significant positive linear trend between maximal oxygen uptake and levels of self-reported PA (55). This is consistent with the sensitivity analysis of cumulative PA performed on our analytical sample (**Supplementary Table S2**). Fifth, we cannot exclude residual confounding by measured or unmeasured variables (e.g. masked hypertension or sex hormones). Finally, the relatively low sample size in our study represents a potential limitation. However, baseline characteristics did not differ between our analytical sample and the total cohort attending the first visit in Tromsø6 ($n = 12{,}981$), which strengthens our external validity to other Northern-European Caucasian adult populations.

In conclusion, higher levels of cumulative PA were associated with increased LADi in males and participants <65 years, and with increased LVMi and LVDi in females. Despite the association between cumulative PA and cardiac chamber enlargement, the function of the heart did not change with higher levels of PA, and the atrioventricular ratio was unchanged. This indicate that cardiac chamber enlargement is a physiological response to PA.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the legal restriction on data availability is set by the Tromsø Study Data and Publication Committee to control for data sharing, including publication of datasets with the potential of reverse identification of deidentified sensitive participant information. The data can however be made available from the Tromsø Study upon application to the Tromsø Study Data and Publication Committee. Requests to access the datasets should be directed to the Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics, Tromsø, Norway (20828/REK Nord). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH, BW, and BM contributed to conception or design of the work. KH drafted the manuscript. All authors contributed to acquisition or analysis of the data. All authors contributed to interpretation of the data, critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.882077/full#supplementary-material

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Paper II

Heitmann KA, Løchen M-L, Hopstock LA, Stylidis M, Welde B, Schirmer H, & Morseth B.

Cross-sectional associations between accelerometry-measured physical activity, left atrial size, and indices of left ventricular diastolic dysfunction: The Tromsø Study.

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Cross-sectional associations between accelerometry-measured physical activity, left atrial size, and indices of left ventricular diastolic dysfunction: The Tromsø Study

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ABSTRACT

Whereas left atrial (LA) enlargement is an independent predictor for adverse cardiovascular events and all-cause mortality, this is regarded a physiological adaption of exercise. Paradoxically, LA size in athletes may overlap the enlargement observed in patients with cardiac pathology. Current knowledge is mainly derived from studies of athletes, and little is known about cardiac adaptations to physical activity (PA) in the general population. We explored the association between objectively measured PA and LA volume index (LAVi), and between LAVi enlargement and indices of diastolic dysfunction stratified by PA-level.

Our study included 1573 participants from the population-based Tromsø Study (2015–16). PA was assessed with an ActiGraph wGT3X-BT accelerometer. Echocardiography was performed according to current guidelines. The associations between PA and LAVi, and between LAVi enlargement and indices of diastolic dysfunction were estimated by univariable and multivariable linear regression analyses, adjusted for sex, age, and cardiovascular risk factors.

Our multiple adjusted analyses showed significant linear associations between PA and LAVi in ages < 70 years, and between PA and LAVi in participants with normal diastolic function. No associations were seen in ages ≥ 70 years or for participants with abnormal diastolic function. In those 40–54 years, the most active participants had larger LAVi (4.45 mL/m^2, $p = 0.016$) than the least active. LAVi enlargement was only associated with indices of diastolic dysfunction in the most inactive participants.

In conclusion, higher levels of PA associate with greater LAVi in participants < 70 years with normal diastolic function. LAVi enlargement is only associated with diastolic dysfunction in the most inactive participants.

1. Introduction

Increasing age is associated with adverse structural and functional changes in the heart, such as left atrial (LA) enlargement (Obas and Vasan, 2018). LA enlargement is an independent predictor for adverse cardiovascular disease (CVD) (Tiwari et al., 2015) and all-cause mortality (Stylidis et al., 2019). Furthermore, LA enlargement is a marker of the severity and chronicity of left ventricular (LV) diastolic dysfunction (Lang et al., 2015), and an important prevention target due to increased risk for heart failure (HF) and CVD events (Gajardo and Llancaqueo, 2019).

Health authorities recommend physical activity (PA) for health promotion and disease prevention, such as CVD and all-cause mortality (Piepoli et al., 2016; Bull et al., 2020; The 2018 Physical Activity Guidelines Advisory Committee, 2018), and improved diastolic and systolic function (Hegde et al., 2016). However, little is known about

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cardiac adaptations to PA in the general adult and elderly population (Joseph et al., 2019); current knowledge is mainly derived from studies of athletes (Hegde et al., 2016). Furthermore, the associations between PA and health outcomes are primarily based on studies using self-reported PA (The 2018 Physical Activity Guidelines Advisory Committee, 2018), which are prone to recall and social desirability biases (Prince et al., 2008).

Exercise-induced cardiac remodelling is considered a benign physiological adaption of athletic training, characterized by chamber enlargements and increased LV wall thickness (D'Ascenzi et al., 2020). Furthermore, a meta-analysis comprising over 7000 elite athletes, reported that athletes had 30% greater LA size compared with sedentary controls, when correcting for body surface area (Iskandar et al., 2015). Paradoxically, LA enlargement in athletes may overlap the LA dilation observed in patients with cardiac pathology, and thus represent a diagnostic challenge for clinicians (D'Ascenzi et al., 2018). The need for future research to investigate the possibility of increased risk associated with high amounts of PA is highlighted (The 2018 Physical Activity Guidelines Advisory Committee, 2018), as the upper and lower limits of PA to exert a beneficial effect is unknown (Piepoli et al., 2016).

We aimed to provide new knowledge on cardiac adaptations to PA in the general adult and elderly population. Our main objectives were to: a) explore the association between objectively measured PA and LA size, and b) investigate if LA enlargement is adversely associated with indices of diastolic dysfunction when correcting for PA. We hypothesized that LA size is associated with PA, and that LA enlargement is not adversely associated with indices of diastolic dysfunction in the most active participants.

2. Methods

2.1. Study population

The Tromsø Study (Jacobsen et al., 2012) is a single center population-based cohort study with seven repeated health surveys of the population of the Tromsø municipality, Northern Norway. This cross-sectional study includes participants from the 7th survey (2015–16) (The Tromsø Study, 2016). All inhabitants ≥ 40 years were invited (n = 32591), with 21,083 men and women participating (65% attendance). The participants completed questionnaires and underwent biological sampling and clinical examinations. Of these, a sample of 8346 participants (randomly assigned or attendees of dual-energy x-ray absorptiometry, echocardiography and eye examination at the 6th survey in 2007–08) participated in a second visit with extended examinations. Among these, 6125 participants provided valid data on accelerometry, and 2340 participants had valid echocardiographic data. In total, 1651 participants had valid data on both echocardiography and accelerometery. Due to missing data for one or more covariates, 78 participants were excluded (height n = 2, systolic blood pressure n = 5, diabetes n = 44, smoking n = 17, low-density lipoprotein (LDL) cholesterol n = 10), leaving an analytical sample of 1573 participants (Table 1).

The present study was approved by the Regional Committee for Medical and Health Research Ethics (2017/1973/REK Nord) and carried out in accordance with the Declaration of Helsinki. All participants signed written informed consent.

2.2. Assessment of PA

PA was assessed objectively in three axes with an accelerometer (wGT3X-BT, ActiGraph LLC, Pensacola, FL, USA) placed on the participants' right hip. The participants were instructed to perform their daily activities as usual, and to wear the accelerometer day and night for eight consecutive days, except during water activities. Valid measurements were defined as wear-time ≥ 10 h/day for ≥ 4 days. Details of the data collection and accelerometer data processing procedures are described elsewhere (Sagelv et al., 2019). The accelerations are expressed as average counts per minute (CPM), and categorized into moderate-to-vigorous PA (MVPA, ≥ 2690 CPM) based on validated cut-points (Sasaki et al., 2011). Steps were collected from acceleration on the vertical axis. The participants' CPM were furthermore divided into PA-quartiles, with the least active quartile 1 as reference: quartile 1 = ≤406 CPM, quartile 2 = 407–514 CPM, quartile 3 = 515–634 CPM and quartile 4 = ≥635 CPM.

Table 1
Descriptive characteristics of the study population by age groups: The Tromsø Study 2015–16.

Variable	40–54 years (n = 305)	55–69 years (n = 729)	≥70 years (n = 539)
Age, years	47.7 (4.4)	63.3 (4.0)	75.7 (4.0)
Gender, % (n) female	59.3 (181)	53.1 (387)	45.8 (247)
Body mass index, kg/m^2	27.1 (5.0)	27.0 (4.2)	27.2 (4.1)
Systolic blood pressure, mmHg	121.9 (16.4)	132.9 (18.8)	143.2 (20.7)
Diastolic blood pressure, mmHg	74.3 (10.3)	76.0 (9.9)	74.3 (9.9)
LDL cholesterol, mmol/L	3.5 (0.9)	3.7 (1.0)	3.3 (1.1)
Smoking, % (n)[a]	55.7 (170)	64.1 (467)	61.4 (331)
Hypertension, untreated, % (n)[b]	17.0 (52)	36.1 (263)	54.2 (292)
Hypertension, controlled, % (n)[c]	4.9 (15)	15.9 (115)	22.6 (121)
Myocardial infarction, % (n)	0 (0)	4.8 (35)	13.3 (70)
Stroke, % (n)	0 (0)	2.6 (19)	6.6 (35)
Diabetes, % (n)	3.6 (11)	5.9 (43)	10.2 (55)
Echocardiography			
LA volume index, mL/m^2	32.0 (9.0)	32.6 (10.9)	37.8 (14.7)
LV mass index male, g/h$^{2.7}$	41.7 (11.3)	46.3 (13.9)	51.8 (18.9)
LV mass index female, g/h$^{2.7}$	36.2 (9.8)	41.2 (12.5)	47.5 (18.6)
e' velocity, lateral, cm/s	12.7 (3.0)	9.6 (2.4)	8.0 (2.4)
e' velocity, septal, cm/s	9.8 (2.2)	7.4 (2.1)	6.2 (2.1)
E/e'ratio	7.5 (2.0)	8.9 (3.4)	11.0 (6.7)
Tricuspid regurgitation velocity, m/s	1.4 (0.7)	1.5 (0.8)	1.7 (0.8)
Ejection fraction < 40%, %	5.8 (15)	6.9 (44)	12.4 (57)
Physical activity			
Mean wear time all valid days, hours	118.0 (15.4)	118.4 (16.1)	113.0 (17.4)
Total PA, CPM	611.6 (174.1)	550.9 (170.4)	449.9 (159.6)
PA-quartile 1, % (n)	9.5 (29)	18.9 (138)	41.9 (226)
PA-quartile 2, % (n)	23.9 (73)	25.4 (185)	25.2 (136)
PA-quartile 3, % (n)	25.2 (77)	27.7 (202)	21.0 (113)
PA-quartile 4, % (n)	41.3 (126)	28.0 (204)	11.9 (64)
MVPA, min/day	53.5 (30.5)	44.5 (29.9)	26.8 (24.9)
Steps, steps/day	8214.5 (2714.3)	7431.7 (2889.9)	5231.3 (2459.3)

LDL: low-density lipoprotein, LA: left atrium, LV: left ventricle, E/e'ratio: ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'), CPM: counts per minute, PA: physical activity, MVPA: moderate-to-vigorous physical activity.
Numbers are mean ± standard deviation or percentage and n.
[a] Smoking: current and previous.
[b] Hypertension, untreated: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and no self-reported use of antihypertensives.
[c] Hypertension, controlled: systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, and self-reported use of antihypertensives.

2.3. Data collection

Data from questionnaires, physical examinations and blood samples were used for the following covariates: Smoking (currently/previously, never), diabetes (currently/previously, no), use of antihypertensives (currently, previously/never), myocardial infarction (previously, no) and stroke (previously, no). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was recorded three times with 1 min interval after 2 min rest, using an automatic

device (Dinamap ProCare 300 monitor, GE Healthcare, Norway), the average from reading two and three was used. Blood samples were analysed for LDL cholesterol at the Department of Laboratory Medicine, University Hospital of North Norway.

2.4. Cardiac structure and function

Echocardiography was performed by a qualified sonographer between August 2015 and October 2016, using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. Offline image readings and analyses were performed by co-author M.S. with the commercially available EchoPac software (Ver. 113, GE Vingmed Ultrasound AS, Horten, Norway). Echocardiographic assessment was performed with the use of standard imaging planes in the left lateral decubitus position according to the joint American and European guidelines (Lang et al., 2015; Nagueh et al., 2016). The echocardiographic assessment was performed on 3–5 consecutive cardiac cycles, and the average was used in the analysis.

LA volume was measured at the end of the LV systole and calculated using the Simpson's biplane method from the apical four- and two chamber views. The LA volume was indexed to body surface area (LAVi) using the Mosteller formula (Mosteller, 1987). Mitral annular e' velocity was measured in apical four-chamber view with pulsed-wave tissue Doppler in both lateral and septal basal regions. Average E/e'ratio was calculated by peak E-wave velocity divided by annular average e' velocity both collected in apical four-chamber view. Tricuspid regurgitation velocity (TRV) was measured as peak modal velocity from the right ventricle to the right atrium during systole, using apical four-chamber view with continuous wave Doppler. LAVi, E/e'ratio, e' velocity and TRV were used to consider diastolic function according to the guidelines (Nagueh et al., 2016). In our analysis, diastolic function was considered as: a) normal if $<$ 50% of the variables were above the cut-offs, or b) abnormal if $\geq$ 50% of the variables were above the cut-offs.

LV myocardial mass was calculated according to the cube formula (Lang et al., 2015), and further indexed to height by raising height to the power of 2.7 (Williams et al., 2018). LV volume was calculated at the end of diastole, using the Simpson's biplane method from the apical four- and two chamber views. Ejection fraction was calculated from the end-diastolic and end-systolic estimates of LV volume, and individuals with ejection fraction $<$ 40% were considered as having HF (Ponikowski et al., 2016). Severity of the mitral and aortic stenosis was assessed by measuring mitral valve area and aortic flow mean pressure gradient, respectively. Mitral regurgitation severity grade was obtained by qualitative estimation of the color Doppler flow jet area. Pressure half-time of regurgitant aortic flow as well as central jet width were used for assessment of the severity of the aortic regurgitation (Zoghbi et al., 2017).

An intra- and inter-observer study was performed on the echocardiography data (Stylidis et al., 2020). Intra-class correlation coefficients on Doppler indices and linear measurements were 0.90–0.99 in the intra-observer study, and 0.84–0.98 in the inter-observer study.

2.5. Statistical methods

The associations between the PA measures and LAVi, and between LAVi enlargement and indices of diastolic function were estimated by univariable and multivariable linear regression analyses. The associations are presented as unstandardized coefficients with 95% confidence intervals (CI). Coefficients for MVPA are presented for every 10 min increase per day (MVPA per 10 min/day), and steps are presented for every 1000 steps per day increase (steps per 1000/day). The multivariable model (Model 2) was adjusted for sex, age, and CVD risk factors (BMI, systolic blood pressure, diabetes, smoking, and LDL cholesterol). In a sub-analysis, we used an extended multivariable model (Model 3), which was adjusted for Model 2 in addition to myocardial infarction, HF, mitral regurgitation, mitral stenosis, aortic regurgitation, and aortic valve flow mean pressure gradient.

In the multivariable model with the PA measures as exposure and LAVi as outcome, we first included stepwise interactions between PA*age, PA*sex, PA*hypertension, PA*BMI, PA* diastolic function, PA*CVD, and PA*LV mass index. We then included only the significant interaction terms (PA*age, and PA*diastolic function) in the multivariable model. We stratified our main analyses by three age groups and diastolic function, as the interactions between PA*age, and PA*diastolic function were significant. All statistical analyses were performed using SPSS version 25 (SPSS Inc., IL, USA), with the alpha level set to 0.05.

3. Results

Descriptive characteristics from questionnaires, biological samplings, clinical examinations, and assessment of PA are given for the participants stratified by age groups in Table 1. The mean age was 64.5 (SD 10.7, range 40–84) years and mean BMI was 27.1 (SD 4.3) kg/m^2. The proportion of men increased with increasing age (p-trend $<$ 0.001), and all measures of PA decreased with increasing age (p-trend $<$ 0.001).

3.1. Association between PA and LAVi

In the overall sample, there was a significant trend towards increasing LAVi with increasing PA-quartiles in the fully adjusted Model 2 (p-trend = 0.017, Table S1). Participants with the highest PA level (quartile 4) had larger LAVi (2.31 mL/m^2, p = 0.015) than participants in quartile 1. LAVi increased non-significantly with increasing MVPA (p = 0.176) and steps (p = 0.184).

We found significant interactions between PA*age, and between PA*diastolic function in the association between PA and LAVi. The association between PA and LAVi showed a positive trend in age groups $<$ 70 years (Fig. 1a-c), whereas no significant association between PA and LAVI among those aged $\geq$ 70. Furthermore, the association between PA and LAVi showed a positive trend in participants with normal diastolic function (Fig. 1d-f), but no significant association between PA and LAVi in participants with abnormal diastolic function. When both the interactions between PA*age, and PA*diastolic function were added to the multiple adjusted Model 2 (Table S2), interactions between PA*age, and PA*diastolic function remained significant (p $<$ 0.05). Therefore, further analyses were stratified by age and diastolic function. The association between PA and LAVi showed a positive trend in participants $<$ 70 years with normal diastolic function, whereas no significant association was observed in participants $\geq$ 70 years or in participants with abnormal diastolic function (Fig. 2).

When stratified by age (Table 2), both models showed positive associations between PA and LAVi in the age groups $<$ 70 years. In those aged 40–54 years, LAVi increased by 0.62 mL/m^2 for every 1000 steps per day increase (p = 0.002). In addition, there was a significant trend showing increased LAVi by increasing PA-quartiles (p-trend = 0.009). LAVi was significantly larger (4.45 mL/m^2, p = 0.016) in participants in PA-quartile 4 vs. quartile 1. In participants aged 55–69 years, LAVi increased by 0.32 mL/m^2 for every 10 min increase in MVPA per day (p = 0.021). There was also a significant trend showing increased LAVi by increasing PA-quartiles (p-trend = 0.007). LAVi was significantly larger (2.93 mL/m^2, p = 0.020) in participants in PA-quartile 4 vs. quartile 1. There were no significant associations between PA and LAVi in participants aged $\geq$ 70 years.

Associations between PA and LAVi stratified by diastolic function showed increased LAVi by increasing PA-quartiles in participants with normal diastolic function (p-trend = 0.002) (Table 3). In participants with normal diastolic function, LAVi was significantly larger (2.77 mL/m^2, p = 0.002) in participants in PA-quartile 4 vs. quartile 1. Furthermore, LAVi increased by 0.22 mL/m^2 for every 10 min increase in MVPA per day (p = 0.033), and by 0.29 mL/m^2 for every 1000 steps per day increase (p = 0.009). There were no significant associations between PA and LAVi in participants with abnormal diastolic function.

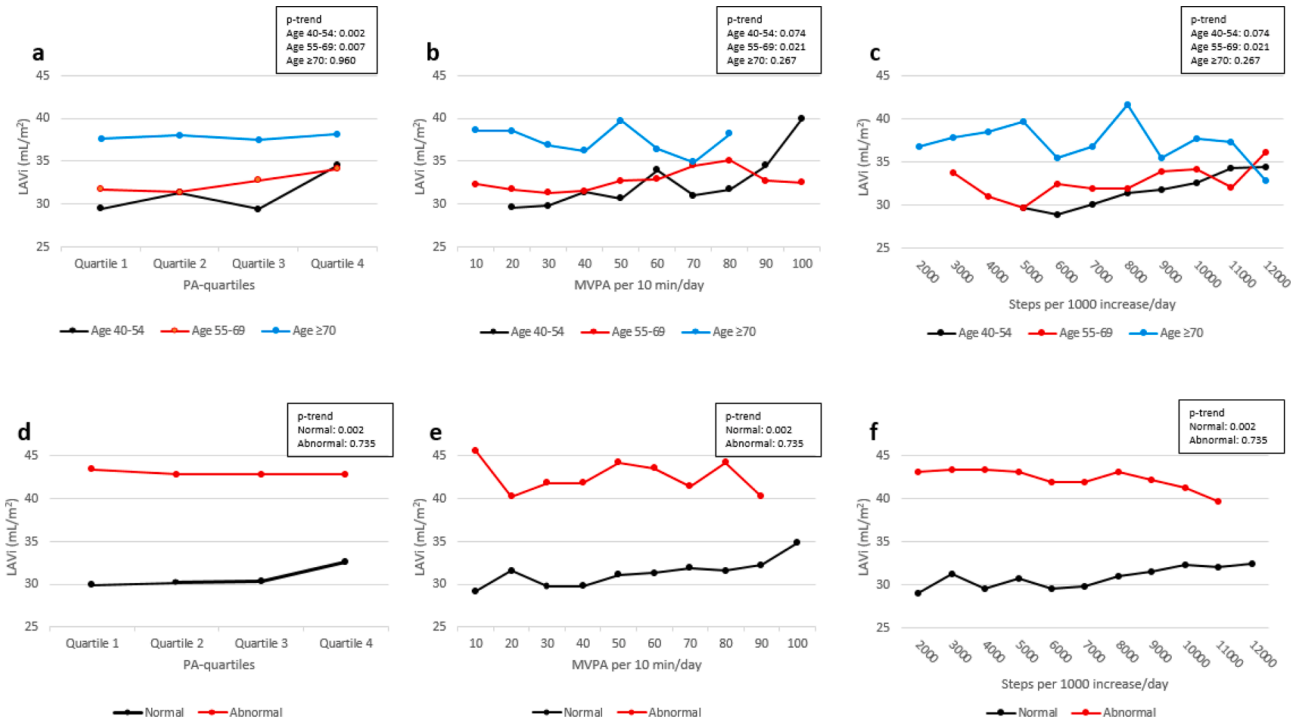

Fig. 1. **a-c** show adjusted mean LAVi stratified by age and PA, and Fig. 1**d-f** show adjusted mean LAVi stratified by LV diastolic function and PA. Fig. 1a and 1d show mean LAVi for the PA-quartiles, where quartile 1 is least active and quartile 4 most active. Fig. 1b and 1e show mean LAVi for every 10 min increase in MVPA per day, and Fig. 1c and 1f show mean LAVi for every 1000 steps per day increase. Mean values were adjusted for sex, BMI, systolic blood pressure, diabetes, smoking, and LDL cholesterol. LAVi: left atrial volume index, PA: physical activity, MVPA: moderate-to-vigorous physical activity, BMI: body mass index, LDL: low-density lipoprotein. The Tromsø Study 2015–16.

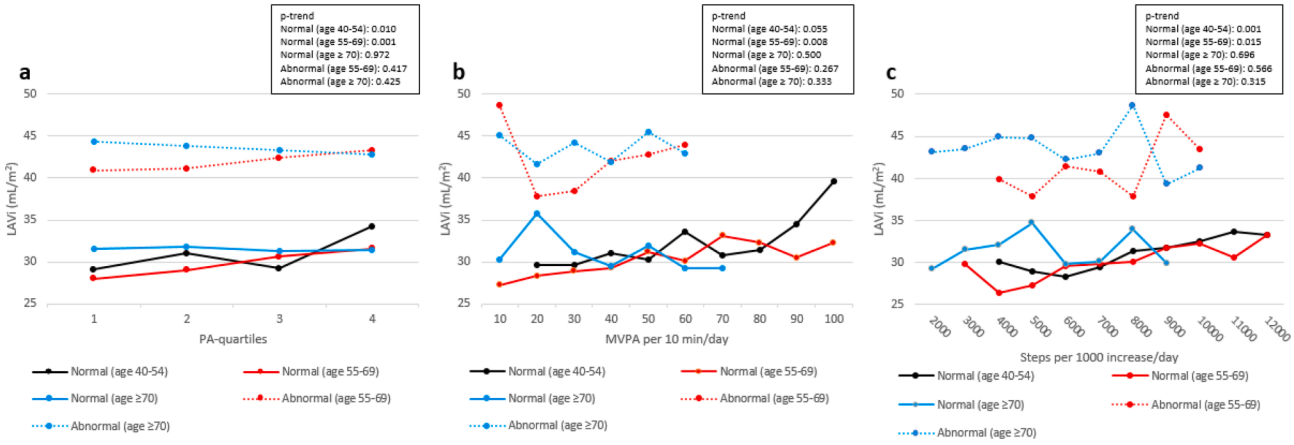

Fig. 2. Adjusted mean LAVi stratified by LV diastolic function, age and PA. Fig. 2a show mean LAVi for the PA-quartiles, where quartile 1 is least active and quartile 4 most active. Fig. 2b show mean LAVi for every 10 min increase in MVPA per day, and Fig. 2c show mean LAVi for every 1000 steps per day increase. Mean values were adjusted for PA level, sex, BMI, systolic blood pressure, diabetes, smoking, and LDL cholesterol. LAVi: left atrial volume index, PA: physical activity, MVPA: moderate-to-vigorous physical activity, BMI: body mass index, LDL: low-density lipoprotein. The Tromsø Study 2015–16.

In general, associations between PA-quartiles and LAVi stratified by hypertension, CVD, LV mass index or sex (Table S3-S6) showed rather similar results as when stratifying for diastolic function. No associations were observed when stratifying by BMI (Table S7). Furthermore, we explored the associations between PA and LAVi using an extended model (Model 3) adjusted for myocardial infarction, HF and valvular disorders in addition to Model 2. In general, we observed similar associations between PA and LAVi as in Model 2, although, some of the associations were slightly stronger in Model 3. As for Model 2, we observed associations between PA and LAVi in participants < 70 years (Table S8), and in participants with normal diastolic function (Table S9). There were no associations between PA and LAVi in participants ≥ 70 years or with abnormal diastolic function.

3.2. *Association between LAVi enlargement and indices of diastolic dysfunction*

LAVi enlargement was associated with unfavorable increase in E/e'ratio (0.24, $p < 0.001$) and TRV (0.02 m/s, $p < 0.001$) for every mL/m^2 increase in the most inactive participants, whereas no associations were seen in higher PA-quartiles (Table S10).

Table 2
Associations between physical activity and left atrial volume index by age (unstandardized coefficients ± 95% CI). The Tromsø Study 2015–16.

	n	LAVi mL/m^2 (SD)	Model 1 β (95% CI)	Model 2 β (95% CI)
Age 40–54				
CPM	297	32.0 (9.0)		
PA-quartile 1	28	29.5 (6.6)	0.00 (Ref.)	0.00 (Ref.)
PA-quartile 2	71	31.3 (11.1)	1.81 (-2.02, 5.65)	1.90 (-1.93, 5.77)
PA-quartile 3	75	29.4 (7.9)	−0.09 (-3.89, 3.71)	0.05 (-3.76, 3.87)
PA-quartile 4	123	34.5 (8.1)	5.05 (1.46, 8.64)	4.45 (0.82, 8.08)
p-trend			0.001	0.009
MVPA per 10 min/day	297	32.0 (9.0)	0.41 (0.08, 0.74)	0.31 (-0.03, 0.65)
p-trend			0.015	0.074
Steps per 1000/day	297	32.0 (9.0)	0.77 (0.40, 1.13)	0.62 (0.23, 1.00)
p-trend			<0.001	0.002
Age 55–69				
CPM	714	32.6 (10.9)		
PA-quartile 1	131	31.7 (12.3)	0.00 (Ref.)	0.00 (Ref.)
PA-quartile 2	184	31.4 (10.0)	−0.36 (-2.81, 2.09)	0.01 (-2.45, 2.47)
PA-quartile 3	199	32.8 (10.6)	1.04 (-1.36, 3.45)	1.30 (-1.12, 3.72)
PA-quartile 4	200	34.1 (10.9)	2.33 (-0.07, 4.74)	2.93 (0.46, 5.41)
p-trend			0.018	0.007
MVPA per 10 min/day	714	32.6 (10.9)	0.33 (0.07, 0.60)	0.32 (0.05, 0.59)
p-trend			0.015	0.021
Steps per 1000/day	714	32.6 (10.9)	0.23 (-0.05, 0.51)	0.26 (-0.03, 0.55)
p-trend			0.110	0.081
Age ≥ 70				
CPM	531	37.8 (14.7)		
PA-quartile 1	224	37.7 (15.4)	0.00 (Ref.)	0.00 (Ref.)
PA-quartile 2	134	38.0 (14.6)	0.34 (-2.83, 3.51)	0.08 (-3.14, 3.29)
PA-quartile 3	110	37.5 (15.1)	−0.19 (-3.57, 3.19)	−0.23 (-3.67, 3.22)
PA-quartile 4	63	38.1 (11.2)	0.39 (-3.75, 4.53)	0.35 (-3.89, 4.58)
p-trend			0.938	0.960
MVPA per 10 min/day	531	37.8 (14.7)	−0.26 (-0.76, 0.24)	−0.30 (-0.82, 0.23)
p-trend			0.312	0.267
Steps per 1000/day	531	37.8 (14.7)	−0.21 (-0.72, 0.30)	−0.24 (-0.78, 0.29)
p-trend			0.425	0.374

LAVi: left atrial volume index, SD: standard deviation, CI: confidence interval, Ref.: reference, CPM: counts per minute, PA: physical activity, MVPA: moderate-to-vigorous physical activity, BMI: body mass index, LDL: low-density lipoprotein.
Model 1 was unadjusted. Model 2 was adjusted for sex, BMI, systolic blood pressure, diabetes, smoking, and LDL cholesterol.

3.3. Sensitivity analysis

When excluding participants with atrial fibrillation (AF, n = 44), we observed similar associations between PA and LAVi, and between LAVi enlargement and indices of diastolic dysfunction as the main results. Therefore, we included participants with AF in our analysis.

4. Discussion

To the best of our knowledge, this is the first study that examined the association between objectively measured PA and LAVi in the general adult and elderly population. Our main findings are that higher levels of PA are associated with greater LAVi, but only in participants < 70 years with normal diastolic function, and that LAVi enlargement is associated with indices of diastolic dysfunction only in the most inactive participants. Our results indicate that LAVi enlargement in physically active individuals is not an expression of cardiac dysfunction.

Table 3
Associations between physical activity and left atrial volume index by left ventricular diastolic function (unstandardized coefficients ± 95% CI). The Tromsø Study 2015–16.

	n	LAVi mL/m^2 (SD)	Model 1 β (95% CI)	Model 2 β (95% CI)
Normal diastolic function[a]				
CPM	1105	30.8 (9.4)		
PA-quartile 1	236	29.9 (10.0)	0.00 (Ref.)	0.00 (Ref.)
PA-quartile 2	281	30.2 (10.2)	0.30 (-1.32, 1.93)	0.42 (-1.25, 2.08)
PA-quartile 3	288	30.4 (9.0)	0.50 (-1.11, 2.12)	0.64 (-1.03, 2.31)
PA-quartile 4	300	32.6 (8.3)	2.77 (1.17, 4.37)	2.77 (1.02, 4.51)
p-trend			0.001	0.002
MVPA per 10 min/day	1105	30.8 (9.4)	0.25 (0.06, 0.43)	0.22 (0.02, 0.42)
p-trend			0.009	0.033
Steps per 1000/day	1105	30.8 (9.4)	0.30 (0.11, 0.48)	0.29 (0.07, 0.50)
p-trend			0.002	0.009
Abnormal diastolic function[b]				
CPM	437	43.0 (14.3)		
PA-quartile 1	147	43.4 (16.2)	0.00 (Ref.)	0.00 (Ref.)
PA-quartile 2	108	42.8 (12.9)	−0.64 (-4.22, 2.94)	−0.66 (-4.29, 2.97)
PA-quartile 3	96	42.8 (14.7)	−0.59 (-4.29, 3.12)	−0.36 (-4.16, 3.44)
PA-quartile 4	86	42.8 (12.2)	−0.67 (-4.50, 3.17)	−0.79 (-4.85, 3.27)
p-trend			0.721	0.735
MVPA per 10 min/day	437	43.0 (14.3)	0.02 (-0.44, 0.49)	−0.02 (-0.52, 0.48)
p-trend			0.925	0.928
Steps per 1000/day	437	43.0 (14.3)	−0.14 (-0.60, 0.33)	−0.18 (-0.70, 0.34)
p-trend			0.567	0.490

LAVi: left atrial volume index, SD: standard deviation, CI: confidence interval, Ref.: reference, CPM: counts per minute, PA: physical activity, MVPA: moderate-to-vigorous physical activity, BMI: body mass index, LDL: low-density lipoprotein.
Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, systolic blood pressure, diabetes, smoking, and LDL cholesterol.
[a] Normal diastolic function = <50% positive variables.
[b] Abnormal diastolic function = ≥50% positive variables.

4.1. PA and LA size

When stratified by age and diastolic function in the same multivariable model, we observed significant trends between PA and LAVi in age groups < 70 years with normal diastolic function only. These findings suggest that the relationship between higher age and increased LA size is mainly explained by diastolic function, as there was no difference between age groups when excluding those with diastolic dysfunction.

Similar to our results, Joseph et al. (2019) reported that PA had greater impact on cardiac alterations in younger than older subjects in the general population. They reported that higher levels of PA improved both systolic and diastolic function (evaluated by longitudinal displacement, e', and myocardial performance index) and lowered resting heart rate in participants ≤ 65 years, whereas there was no effect of PA in those > 65 years. Furthermore, the authors suggested that there is a cut-off point in age, where the beneficial effects of PA ceases.

The positive association between PA and LAVi observed in our study is widely supported by previous studies on athletes (Iskandar et al., 2015; Pelliccia et al., 2005). In addition, the association between exercise and LAVi has been demonstrated in adolescent endurance athletes (Hoogsteen et al., 2003). In the general adult population, the association between cardiorespiratory fitness and LAVi (Letnes et al., 2020), and the association between objectively measured PA and LA dimension has been demonstrated (Andersson et al., 2015). Furthermore, the relationship between exercise and LAVi has also been confirmed in a randomized controlled trial with middle-aged adults (Opondo et al., 2018). In contrast to our results, Bjerring et al. (2018) found no association between exercise and LAVi although they observed other associations between exercise and cardiac remodelling in preadolescent athletes. The lack of significant association between exercise and LAVi may be due to the participants' young age, and because atrial remodelling depends on years of training (D'Andrea et al., 2010).

Enlarged LAVi is considered a normal physiological adaptation to exercise in athletes, and it is well documented that the cardiac chambers increase by exercise (Iskandar et al., 2015; Pelliccia et al., 2005). Enlarged chambers and the accompanying capability to generate a large stroke volume are the main alterations by exercise-induced cardiac remodelling (Weiner and Baggish, 2012), and a large stroke volume is essential for athletic endurance and performance (Bassett and Howley, 2000). Our results indicate that the exercise-induced cardiac adaptations start at lower levels of PA than the typical training load of an athlete, and that exercise-induced LA remodelling also affects the general and elderly population.

In athletes, it has been demonstrated that LA enlargement is not necessarily associated with LA dysfunction (D'Ascenzi et al., 2011). In fact, supernormal LV diastolic function has been documented in athletes with LA enlargement (D'Ascenzi et al., 2011). These athletes typically have normal reservoir function and reduced LA active contraction (D'Ascenzi et al., 2018). Reduced LA active contraction represents a more efficient filling of the heart, due to larger contribution from passive hemodynamic instead of active contractions (Lakatos et al., 2020). These documented improvements in LA function supports our results that LAVi enlargement in physically active individuals is benign.

The physiological mechanisms triggering LA remodelling in athletes are the increased hemodynamic stress on the walls due to increased stroke volume and cardiac output during exercise (D'Ascenzi et al., 2018). In contrast, LA enlargement may also reflect the presence of LA dysfunction and increased filling pressures over time (D'Ascenzi et al., 2020; Nagueh et al., 2016). Furthermore, LA enlargement is seen in subjects with AF and valvular disease (Nagueh et al., 2016). However, in our study population only a few participants had AF, and sensitivity analysis revealed that the associations between PA and LAVi were almost unchanged if they were included or not. Also, adjustment for valvular disease and HF did not change the associations between PA and LAVi. This suggests that enlarged LAVi with increasing levels of PA is due to exercise-induced LA remodelling.

4.2. LA enlargement and indices of diastolic dysfunction

We observed an association between LAVi enlargement and increased E/e'ratio and TRV among the most inactive participants only. This finding is of importance as increased E/e'ratio is associated with CVD, all-cause mortality and HF (Mitter et al., 2017). Also, elevated TRV indicates elevated LV filling pressure, and is a main criteria for determining LV diastolic dysfunction (Nagueh et al., 2016). However, as mean TRV was 1.8 m/s in the most inactive participants, the insufficiency was well within the border of a normal TRV (Nagueh et al., 2016).

Our results are supported by previous literature which have demonstrated lower E/e'ratio with higher levels of PA (D'Ascenzi et al., 2011), and that older participants reporting ideal levels of PA have lower E/e'ratio compared to those who reported low PA (Hegde et al., 2016). Furthermore, it has been demonstrated that low cardiorespiratory fitness is associated with higher E/e'ratio, compared with higher levels of fitness (Brinker et al., 2014). In contrast, some researchers have reported no association between LAVi and E/e'ratio or TRV (Letnes et al., 2020), or between PA and E/e'ratio (Andersson et al., 2015) in healthy adults or middle-aged. This discrepancy may be explained by a younger and healthier population in these studies. It is suggested that the age-related changes in diastolic function are probably not developed in young cohorts (Hegde et al., 2016).

Furthermore, LA enlargement is an independent risk factor for AF in the general population (Pelliccia et al., 2005). Although it is well documented that moderate levels of PA decreases the risk of AF (Valenzuela et al., 2020), vigorous endurance exercise may be associated with increased risk of AF (D'Ascenzi et al., 2015). However, solid evidence for exercise-induced LA enlargement as a substrate for AF is lacking (D'Ascenzi et al., 2015). Furthermore, in a large study of 1800 competitive athletes, the authors demonstrated frequently LA enlargement, but low prevalence of AF (<1%) (Pelliccia et al., 2005).

4.3. Strengths and limitations

The main strength of this study is the combined use of objectively measured PA and echocardiography in a large study population with a wide age span. Our large study population of adult and elderly individuals represents the general population. Self-reported PA is prone to both recall- and social desirability bias (Prince et al., 2008), and is neither able to capture light PA or assess MVPA precisely (The 2018 Physical Activity Guidelines Advisory Committee, 2018). In contrast, device based measured PA provides objective and more valid data across the whole spectrum of PA as well as total accumulated PA throughout the day (Chomistek et al., 2017). The echocardiography was conducted according to current guidelines, and we used the recommended LAVi calculated with the Simpson's biplane method to assess LA size (Lang et al., 2015).

Potential limitations should be addressed. Firstly, the cross-sectional study design prevents evaluation of longitudinal changes in PA and LA size, or intra-subject LA remodelling, and we cannot establish direction of the association or causation. Secondly, lack of data on LA function prevents extensive evaluation of the association between PA and LA remodelling. Thirdly, lack of data from cardiopulmonary exercise-testing prevents us from evaluating the impact of cardiorespiratory fitness on LA remodelling. Fourthly, although we adjusted for covariates, we cannot exclude the possibility of residual confounding. Fifth, due to few participants with diastolic dysfunction, diastolic function was dichotomized into normal or abnormal. This may have underestimated the influence of diastolic dysfunction on LAVi, as the indeterminate cases (=50% positive variables) were defined as abnormal. Lastly, as the accelerometer fails to register water-based activities and is less accurate in movements involving small trunk motions (e.g. bicycling), the participant's true PA is probably somewhat underestimated.

In conclusion, increasing level of PA was associated with greater LAVi in the general adult and elderly population < 70 years with normal LV diastolic function, whereas no associations were seen at ages ≥ 70 years or for participants with abnormal diastolic function. Furthermore, LAVi enlargement was only associated with diastolic dysfunction in the most inactive PA-quartile. The beneficial effect of PA on indices of LV diastolic dysfunction was observed from PA-quartile 2, with no additional benefits from increasing PA.

CRediT authorship contribution statement

Kim Arne Heitmann: Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Visualization. **Maja-Lisa Løchen:** Conceptualization, Methodology, Validation, Writing - review & editing. **Laila A. Hopstock:** Methodology, Validation, Investigation, Writing - review & editing. **Michael Stylidis:** Conceptualization,

Methodology, Validation, Investigation, Writing - review & editing. **Boye Welde:** Validation, Writing - review & editing. **Henrik Schirmer:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing. **Bente Morseth:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author's contributions

KAH, MLL, HS, MS and BM contributed to conception or design of the work. All authors contributed to acquisition, analysis or interpretation of the data. KAH drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Appendix A. Supplementary data

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Paper III

Heitmann KA, Løchen M-L, Stylidis M, Hopstock LA, Schirmer H, & Morseth B.

Associations between physical activity, left atrial size and incident atrial fibrillation: the Tromsø Study 1994-2016.

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Associations between physical activity, left atrial size and incident atrial fibrillation: the Tromsø Study 1994–2016

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ABSTRACT

Aims Left atrial (LA) enlargement is an independent risk factor for atrial fibrillation (AF). Interestingly, some athletes have increased risk of AF, which may be linked to LA enlargement; however, little is known about the relationship between LA enlargement and AF risk at moderate-level physical activity (PA). We aimed to explore the associations between PA, LA size and risk of incident AF, and if PA can attenuate the risk of AF with LA enlargement.

Methods This prospective study followed 2479 participants (52.4% female), free from known cardiac pathology, for median 20.2 years. Participants were followed up for hospital-diagnosed AF, confirmed by electrocardiography, from 1994-95 through 2016. At baseline, LA size was evaluated by anteroposterior LA diameter, and PA was self-reported by questionnaire.

Results We observed a U-shaped relationship between PA and AF, and moderately active had 32% lower AF risk than inactive ($HR_{adjusted}$ 0.68, 95% CI 0.50 to 0.93). Participants with LA enlargement had 38% higher AF risk compared with participants with normal LA size ($HR_{adjusted}$ 1.38, 95% CI 1.12 to 1.69). However, the increased AF risk with LA enlargement was attenuated by PA; compared with inactive participants with LA enlargement, the AF risk was 45% lower among active with LA enlargement ($HR_{adjusted}$ 0.55, 95% CI 0.39 to 0.79). AF risk in active participants with LA enlargement did not differ from active with normal LA size. These patterns were observed in both men and women, and in participants over/under 65 years.

Conclusion Moderate PA was associated with reduced AF risk, and PA attenuated the increased risk of AF with LA enlargement in both men and women and all age groups.

Key questions

What is already known about this subject?

- Left atrial (LA) enlargement is an independent risk factor for atrial fibrillation (AF).
- Moderate physical activity (PA) is associated with reduced risk of cardiovascular disease including AF.
- Little is known about the role of moderate PA in the association between LA size and risk of AF in the general population.

What does this study add?

- In this prospective study, PA was associated with lower risk of AF in a U-shaped pattern.
- Participants with LA enlargement had higher AF risk compared with participants with normal LA size.
- PA attenuated the increased risk of AF with LA enlargement in both men and women and all age groups.

How might this impact on clinical practice?

- We suggest that the protective effect of moderate PA outweighs the potential risk of AF with LA enlargement.
- Increased understanding of the relationship between PA and AF may guide clinicians in implementing PA in primary and secondary prevention of AF.

INTRODUCTION

Atrial fibrillation (AF) is the most common clinical arrhythmia worldwide, associated with considerably morbidity, such as stroke and heart failure.[1] In 2016, the global prevalence of AF was 43.6 million, and lifetime risk for developing AF in Europeans over 55 years is approximately one in three.[1] Furthermore, the risk of AF increases with ageing, and due to increased longevity in the general population, a twofold increase in AF is expected during the next decades.[1] Thus, more knowledge on modifiable risk factors for prevention of AF is needed.

Physical activity (PA) is recommended for health promotion and disease prevention,[2] and it is well documented that PA is associated with reduced risk of cardiovascular disease including AF[1 3] and all-cause mortality.[4] Paradoxically, studies have reported that high amounts of vigorous exercise may attenuate the benefits of moderate PA, or even increase the risk of AF.[5 6] Studies have demonstrated that the risk of AF increases with high levels of lifelong exercise, or participation in endurance sports,[7 8] and that elite athletes more frequently experience AF than non-athletes.[9]

Several studies have reported that left atrial (LA) enlargement is an independent risk factor for AF in the general population,[8 10 11]

and pathological conditions that increase LA size (eg, hypertension, valvular heart disease and heart failure) further increase the risk of AF.[12] In addition to increased risk of AF, LA enlargement is a risk factor for stroke and all-cause mortality[13 14] in the general population. Additionally, LA size increases with exercise,[15] and studies have observed that LA size is larger in both athletes[16] and in active adult and elderly individuals.[17] Some elite athletes even have LA enlargement overlapping LA size seen in cardiac pathology.[18] The mechanisms underlying the association between exercise and AF are not established, but it is suggested that the increased risk of AF with extensive endurance exercise may be linked to LA enlargement.[19]

However, despite increased risk of AF with both LA enlargement and with vigorous exercise, convincing data linking the combination of exercise and LA size to AF are lacking and are largely speculative.[19 20] Furthermore, studies have demonstrated that LA function is preserved,[18] or even improved in athletes with LA enlargement.[15] Also, LA enlargement has been reported in endurance athletes, without correlation with electrophysiologic remodelling.[21] Thus, it is of importance to elucidate if LA enlargement is a benign physiological adaption of PA and exercise, or part of a pathophysiological mechanism increasing the risk of AF.

Current knowledge of the relationship between exercise, LA remodelling and AF is mainly derived from studies of athletes. Thus, little is known about the role of moderate PA in the association between LA size and risk of AF in the general population. Therefore, our objective was to explore the associations between PA, LA size and incident risk of AF in a general adult and elderly population. Furthermore, we aimed to explore if PA attenuates the increased risk of AF seen with LA enlargement.

METHODS

Study population

The Tromsø Study is a single-centre population-based cohort study with seven repeated health surveys of the population of the Tromsø municipality, Norway.[22] The present study includes participants from the fourth survey of the Tromsø Study (Tromsø4, 1994–1995), with 22 years follow-up for AF until 31 December 2016.

In Tromsø4, all inhabitants ≥25 years were invited (n=37 558), with 27 158 men and women attending the first visit (77% attendance). Of these, all men aged 55–74 years, all women aged 50–74 years and 5%–8% random samples of the other age groups aged <85 years were invited to a second visit with extended examinations. Of these, a total of 7965 participants (76% of the 10 542 invited) attended the second visit. These participants were alternately allocated by computer to one of two lines of examination when attending the first visit, and 3287 participants in one of the lines were examined by echocardiography. These participants did not differ from the total sample attending the second visit.[23]

In total, 2714 participants provided valid data on PA in combination with valid echocardiography data and status of myocardial infarction at baseline. We excluded participants with previous or present documented AF (n=45), valvular heart disease (n=27), left ventricular (LV) ejection fraction <40% (n=13), previous myocardial infarction (n=129) and LA below normal reference range (n=16) at baseline. Furthermore, one participant was excluded due to missing data on a covariate (systolic blood pressure). Finally, our analytical sample consisted of 2479 participants free from known cardiac pathology, with valid data on PA, AF, echocardiography and covariates at baseline (table 1).

Assessment of PA

PA was assessed by a validated questionnaire measuring duration of light and hard leisure time PA,[24] which has been used in the Norwegian health surveys constituting The Cohort of Norway.[25] The PA questionnaire was used to assess the weekly average hours with light (not sweating or out of breath) and hard leisure time PA (sweating/out of breath), respectively, over the last year. In this study, we used the question about hard PA in the main analyses: (1) 0 hours/week (inactive), (2) 0–1 hour/week (low), (3) 1–2 hours/week (moderate), (4) ≥3 hours/week (vigorous). Time spent going to/from work was considered as leisure-time PA. In some analyses, hard leisure-time PA is dichotomised into inactive (0 hours/week; option 1) and active (>0 hours/week; option 2–4).

For sensitivity analysis, we combined questions about light and hard PA into five categories: (1) light and hard PA 0 hours/week (sedentary), (2) light PA >0 hours/week and hard PA 0 hours/week (inactive), (3) hard PA 0–1 hour/week (low), (4) hard PA 1–2 hours/week (moderate), (5) hard PA ≥3 hours/week (vigorous).

Cardiac structure and function

Echocardiography was performed by three medical doctors (one trained in echocardiography and two expert cardiologists), using a VingMed CFM 750 ultrasound scanner (VingMed Sound A/S, Horten, Norway). The echocardiographic assessment was performed with the use of standard imaging planes in a supine left lateral position. The echocardiographic assessment was performed online in one heart cycle, but remeasured if deviating from eye-balled estimates. Procedures and details of echocardiographic assessments in Tromsø4 are described elsewhere.[23]

LA anteroposterior diameter was measured at the end of the LV systole by M-mode echocardiography in the parasternal short axis view at the aortic valve level, after alignment of LV in long axis view, using the leading edge-to-leading edge convention.[26] LA diameter was indexed to body surface area[27] and presented as centimetres per metre squared (cm/m^2). LA diameter index was categorised into small (<1.5 cm/m^2), normal (1.5–2.3 cm/m^2) and enlarged (≥2.3 cm/m^2).[26] LV dimensions were measured at the end of diastole and systole, in

Table 1 Baseline and follow-up characteristics stratified by PA: the Tromsø Study 1994–1995

	Inactive (n=1502)	Active (n=977)	Total (n=2479)
Baseline characteristics			
Age, years	60.8 (9.3)	55.1 (11.9)	58.6 (10.7)
Sex, % (n) female	61.6 (925)	38.2 (373)	52.4 (1298)
Body mass index, kg/m^2	25.9 (4.0)	25.5 (3.3)	25.8 (3.8)
Systolic blood pressure, mm Hg	145.1 (22.3)	140.0 (20.5)	143.1 (21.8)
Diastolic blood pressure, mm Hg	83.2 (12.5)	81.7 (12.3)	82.6 (12.4)
Heart rate rest, beats/min	71.7 (12.1)	69.0 (12.1)	70.6 (12.2)
LDL cholesterol, mmol/L	5.2 (1.3)	4.9 (1.3)	5.1 (1.3)
C-reactive protein, mg/L	2.7 (6.1)	2.3 (7.1)	2.6 (6.5)
Antihypertensives, % (n)	12.3 (184)	7.1 (69)	10.3 (253)
Hypertension, controlled, % (n)	1.9 (29)	1.3 (13)	1.7 (42)
Hypertension, uncontrolled, % (n)	10.3 (155)	5.7 (56)	8.5 (211)
Hypertension, untreated, % (n)	46.5 (699)	42.0 (410)	44.7 (1109)
Stroke, % (n)	2.1 (31)	1.1 (11)	1.7 (42)
Diabetes, % (n)	2.7 (40)	1.4 (14)	2.2 (54)
Palpitations, % (n)	24.4 (309)	20.5 (185)	22.8 (494)
Thyroid disease, % (n)	5.4 (81)	3.9 (38)	5.5 (119)
Smoking, % (n)	33.6 (504)	27.7 (271)	31.3 (775)
Alcohol, glasses/14 days	3.6 (5.9)	5.2 (7.0)	4.2 (6.5)
Coffee, cups/day	5.4 (3.2)	5.5 (3.6)	5.5 (3.4)
LV mass index, g/h$^{2.7}$	44.4 (12.3)	42.9 (12.1)	43.8 (12.2)
LV mass index, g/h$^{2.7}$ female	43.6 (12.0)	39.4 (10.5)	42.4 (11.8)
LV mass index, g/h$^{2.7}$ male	45.7 (12.6)	45.0 (12.5)	45.4 (12.5)
LA diameter, cm	3.9 (0.6)	4.0 (0.6)	4.0 (0.6)
LA diameter, cm female	3.8 (0.6)	3.7 (0.5)	3.8 (0.5)
LA diameter, cm male	4.1 (0.6)	4.2 (0.5)	4.2 (0.6)
LA diameter index, cm/m^2	2.2 (0.3)	2.1 (0.3)	2.2 (0.3)
LA diameter index, cm/m^2 female	2.2 (0.3)	2.2 (0.3)	2.2 (0.3)
LA diameter index, cm/m^2 male	2.1 (0.3)	2.1 (0.3)	2.1 (0.3)
Physical activity *			
Inactive, % (n)	100 (1502)	0.0 (0)	60.6 (1502)
Low, % (n)	0.0 (0)	39.2 (383)	15.4 (383)
Moderate, % (n)	0.0 (0)	40.0 (391)	15.8 (391)
Vigorous, % (n)	0.0 (0)	20.8 (203)	8.2 (203)
Follow-up characteristics			
AF during follow-up, % (n)	17.9 (269)	13.3 (130)	16.1 (399)
Follow-up time, years	15.9 (6.7)	17.6 (6.2)	16.6 (6.6)

Numbers are mean±SD or percentage and n.
*Hard leisure time PA, weekly average over the last year.
AF, atrial fibrillation; LA, left atrial; LDL, low-density lipoprotein; LV, left ventricular; PA, physical activity.

the parasternal short axis view, after alignment of LV in long axis view to the leading edge-to-edge convention.[26] LV ejection fraction was calculated by the Teichholz formula,[28] using end-diastolic and end-systolic LV dimensions. LV myocardial mass was calculated according to the cube formula[26] and further indexed to height raised to the allometric power of 2.7.[29]

Valvular heart disease was defined by of the following criteria: (a) mitral stenosis identified by pulsed Doppler, (b) aortic stenosis (peak gradient >36 mm Hg) by

continuous Doppler, (c) mitral regurgitation (regurgitant jet area >7 cm^2) by two-dimensional colour Doppler imaging and/or (d) aortic regurgitation (vena contracta width >50% of LV outflow tract, or colour jet exceeding mitral valve coaptation point), by colour M-mode.

A reproducibility study was performed by the two main observers in a subsample of 49 subjects.[23] Intraobserver differences (mean±SD) for LV mass were 3.0±39.0 g and 7.0±25.5 g, respectively, whereas interobserver difference was 14.8±32.5 g.

Covariates

Baseline data from Tromsø4 include the following covariate extracted from self-reported questionnaires, physical examinations and blood samples: daily cigarette smoking (yes/no), coffee consumption (cups/day), diabetes (yes/no), use of antihypertensives (currently or previously/never), myocardial infarction (previously/no), stroke (previously/no), thyroid disease (yes/no) and palpitations (yes/no). Alcohol consumption was summarised from three questions reporting number of glasses of beer, wine or spirit normally consumed within a 14-day period.

Heart rate and blood pressure were recorded three times with 1 min intervals after 2 min seated rest, by specially trained nurses using an automatic device (Dinamap Vital Signs 1846 monitor, Criticon, Florida). For resting heart rate, the lowest recorded reading was used. For blood pressure, the average from reading two and three was used. Blood pressure was classified into hypertension groups: (a) normotensive (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg and no self-reported use of antihypertensives), (b) hypertensive, controlled (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg and self-reported use of antihypertensives), (c) hypertensive, uncontrolled (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and self-reported use of antihypertensives) or (d) hypertension, untreated (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and no self-reported use of antihypertensives). Height and weight were measured with participants wearing light clothing and no shoes. Body mass index was calculated as weight (kg) divided by height squared (m^2).

Blood samples were analysed for total and high-density lipoprotein cholesterol (mmol/L) and C-reactive protein (mg/L) at the Department of Clinical Chemistry, University Hospital of North Norway. Low-density lipoprotein (LDL) cholesterol was estimated by subtracting high-density lipoprotein cholesterol from total cholesterol.

Follow-up and detection of AF

The participants were followed from the date of examination in 1994–95 (Tromsø4), until (a) the date of first documented AF, (b) date of censoring due to death or migration or (c) end of follow-up on 31 December 2016, whichever came first.

The follow-up data on AF were derived from the diagnosis registry of the University Hospital of North Norway, the only hospital in the region, by linking the hospital records of AF to the participants' unique Norwegian national 11-digit identification number. Hospital records were searched for incident cases of AF confirmed by electrocardiography confirmation. Additionally, in participants with diagnoses of cerebrovascular or cardiovascular events, but without diagnosis of arrhythmias, hospital records were manually searched for notes on AF. Details of ascertainment of AF are described elsewhere.[30] The events were evaluated and adjudicated by an independent expert endpoint committee. Postoperative AF within 28 days after surgery, myocardial infarction or other acute cardiac events, as well as AF documented the last week of life, were all classified as non-cases.

Statistical methods

Characteristics of the study population are presented as means with SD or percentages with number of observations (n). Associations between PA, LA size and AF risk were evaluated using univariable and multivariable Cox proportional hazard regression analyses. The associations are presented as HRs with 95% CI. The proportional hazard assumption was confirmed by visual inspection of log-minus-log plots. Model 1 was unadjusted, model 2 was adjusted for age, sex, body mass index and systolic blood pressure.

To test the robustness of the fully adjusted model 2, we performed sensitivity analyses with additional covariates (smoking, coffee consumption, diabetes, LDL cholesterol, palpitations, LV myocardial mass index, thyroid disease, C reactive protein, alcohol consumption and resting heart rate) stepwise, or jointly, added to the model.

In the fully adjusted model 2, we tested for possible interactions between PA*sex, PA*age, PA*hypertension groups, PA*body mass index and PA*LA size in a stepwise analysis of the association between PA and AF. We observed a significant interaction between PA*LA size ($p=0.023$), whereas no significant interactions were indicated for the other interaction terms ($p>0.50$). However, given previously reported age and sex differences in the association between PA and AF risk, we also stratified our main analyses by sex and age in addition to LA size.

All statistical analyses were performed using SPSS V.26 (SPSS, Illinois, USA), with a two-sided $p\leq0.05$ considered statistically significant.

RESULTS

In total, 1181 men (57.7±10.7 years) and 1298 women (59.3±10.7 years), 25–83 years, were included in our analyses. Of these, 399 participants (214 men and 185 women) were diagnosed with AF during a mean follow-up of 16.6±6.6 years (median 20.2 years, IQR 11.6–21.9 years). Descriptive characteristics for the participants stratified by level of PA are presented in table 1.

Table 2 Association between PA and AF (HR ±95% CI): the Tromsø Study 1994–1995

	N (n=2479)	AF events, % (n)	Person-years (mean±SD)	Model 1, HR (95% CI)	Model 1, P-value	Model 2, HR (95% CI)	Model 2, P-value
Inactive	1502	17.9 (269)	15.9 (6.7)	1.00 (ref.)		1.00 (ref.)	
Low	383	13.1 (50)	17.4 (6.5)	0.64 (0.47 to 0.87)	0.004	0.80 (0.59 to 1.09)	0.150
Moderate	391	12.3 (48)	17.8 (6.0)	0.59 (0.43 to 0.80)	0.001	0.68 (0.50 to 0.93)	0.017
Vigorous	203	15.8 (32)	17.7 (6.1)	0.76 (0.53 to 1.09)	0.138	0.87 (0.60 to 1.27)	0.473

Model 1 was unadjusted. Model 2 was adjusted for age, sex, body mass index and systolic blood pressure.
AF, atrial fibrillation; PA, physical activity; ref., reference.

Overall, we observed 32% lower risk of AF in moderately active than in inactive participants ($HR_{adjusted}$ 0.68, 95% CI 0.50 to 0.93), and a U-shaped relationship was observed (table 2). Furthermore, participants with LA enlargement had 38% higher risk of AF compared with participants with normal LA size ($HR_{adjusted}$ 1.38, 95% CI 1.12 to 1.69).

In analyses stratified by LA size (table 3), we observed that PA was associated with lower risk of AF in participants with LA enlargement only, but significantly reduced only in the low PA group ($HR_{adjusted}$ 0.41, 95% CI 0.22 to 0.77). Adjusted cumulative hazard for AF stratified by joint associations of PA and LA size is presented in figure 1. The increased AF risk with LA enlargement was attenuated by PA; compared with inactive participants with LA enlargement, the risk of AF was 45% lower among active with LA enlargement ($HR_{adjusted}$ 0.55, 95% CI 0.39 to 0.79). Furthermore, the risk of AF in active participants with LA enlargement did not differ from participants with normal LA size (online supplemental table S1).

In sex stratified analyses, we observed 79% higher risk of AF in men than in women ($HR_{adjusted}$ 1.79, 95% CI 1.47 to 2.19) (online supplemental table S2). Adjusted cumulative hazard for AF stratified by joint associations of PA and LA size, and sex, is presented in figure 2. In both women and men, active participants with LA enlargement had the same risk of AF as participants with normal LA size (online supplemental table S2).

When we stratified by age, participants ≥65 years had 2.6-fold higher risk of AF compared with participants <65 years ($HR_{adjusted}$ 2.59, 95% CI 2.09 to 3.20) (online supplemental table S3). Adjusted cumulative hazard for AF stratified by joint associations of PA and LA size, and age, is presented in figure 3. The risk of AF in active with LA enlargement was not higher in any age groups compared with participants with normal LA size (online supplemental table S3).

Adjusted cumulative hazard for AF stratified by joint associations of PA, LA size and age, stratified by sex, is presented in online supplemental figure S1 and table S4). In general, men and women <65 years showed the lowest risk of AF compared with inactive ≥65 years with LA enlargement, which had the highest risk of AF. Moreover, in both men and women <65 years, the risk of AF was similar in active with LA enlargement as in those with normal LA size (online supplemental table S5).

Sensitivity analysis

When we combined questions about light and hard PA into five categories (online supplemental table S6), the association between PA and AF was similar as in the main analyses with four levels of hard PA (table 2).

Table 3 Associations between PA and AF stratified by LA size (HR ±95% CI): the Tromsø Study 1994–1995

	N (n=2479)	AF events, % (n)	Person-years (mean±SD)	Model 1, HR (95% CI)	Model 1, P-value	Model 2, HR (95% CI)	Model 2, P-value
LA normal	1714	13.6 (233)	17.0 (6.5)				
Inactive	1019	14.3 (146)	16.4 (6.7)	1.00 (ref.)		1.00 (ref.)	
Low	279	14.0 (39)	17.5 (6.6)	0.88 (0.62 to 1.26)	0.488	1.07 (0.75 to 1.54)	0.707
Moderate	286	10.1 (29)	18.2 (5.9)	0.61 (0.41 to 0.91)	0.015	0.73 (0.49 to 1.09)	0.125
Vigorous	130	14.6 (19)	17.9 (6.2)	0.91 (0.56 to 1.46)	0.681	1.05 (0.65 to 1.71)	0.837
LA enlarged	765	21.7 (166)	15.7 (6.6)				
Inactive	483	25.5 (123)	14.9 (6.7)	1.00 (ref.)		1.00 (ref.)	
Low	104	10.6 (11)	17.1 (6.2)	0.34 (0.18 to 0.63)	0.001	0.41 (0.22 to 0.77)	0.005
Moderate	105	18.1 (19)	16.8 (6.2)	0.60 (0.37 to 0.98)	0.041	0.62 (0.38 to 1.02)	0.061
Vigorous	73	17.8 (13)	17.5 (6.1)	0.56 (0.32 to 0.99)	0.047	0.62 (0.34 to 1.12)	0.113

Model 1 was unadjusted. Model 2 was adjusted for age, sex, body mass index and systolic blood pressure.
PA, physical activity; LA, left atrial/left atrium; AF, atrial fibrillation; ref., reference.;

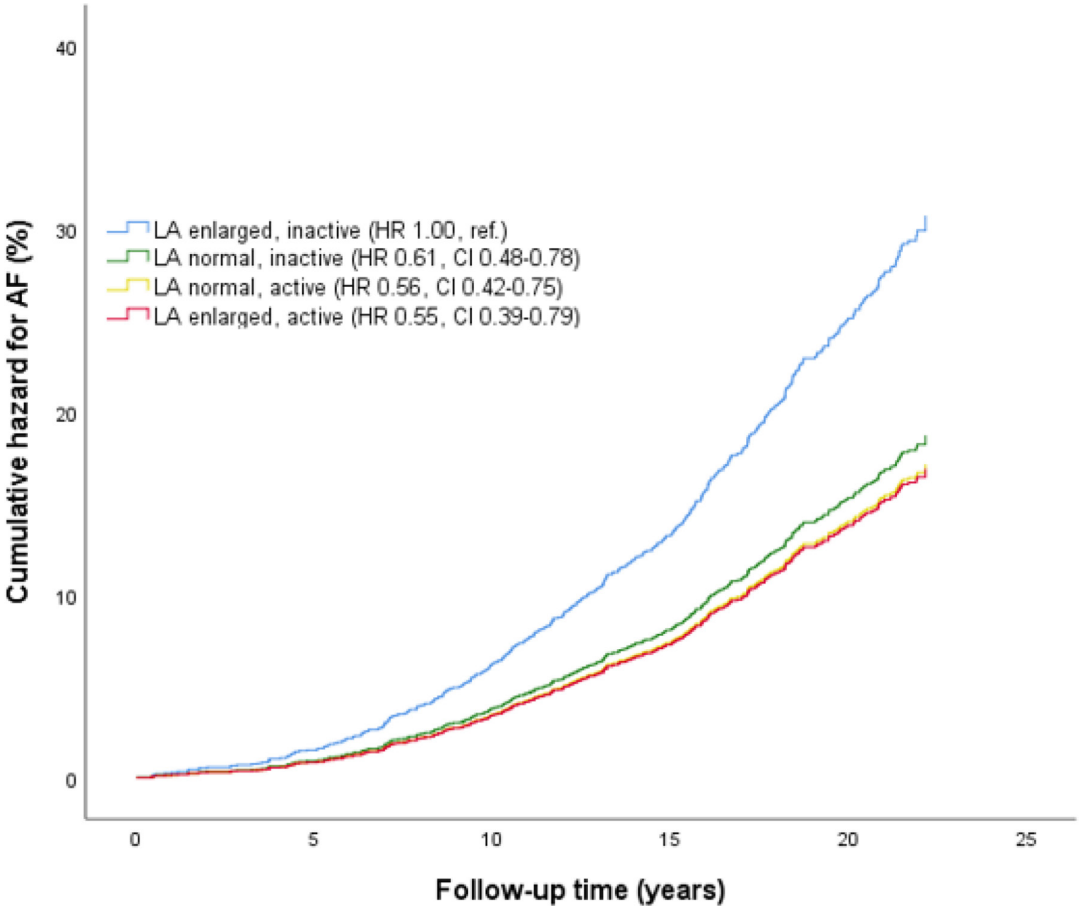

Figure 1 Adjusted cumulative hazard for AF by joint associations of PA and LA size with AF risk. Differences between groups are indicated with HR and 95% CI. The model is adjusted for age, sex, body mass index and systolic blood pressure. AF, atrial fibrillation, LA, left atrial/left atrium. The Tromsø Study 1994–1995.

Furthermore, the association between PA and AF did not change when we replaced systolic blood pressure (model 2) with hypertension groups (online supplemental table S7, model 3). Similarly, the association between PA and AF did not differ from model two when additional covariates (smoking, coffee consumption, diabetes, LDL cholesterol, palpitations, LV myocardial mass index, thyroid disease, C-reactive protein, alcohol consumption or resting heart rate) were added (online supplemental table S8, Model 3).

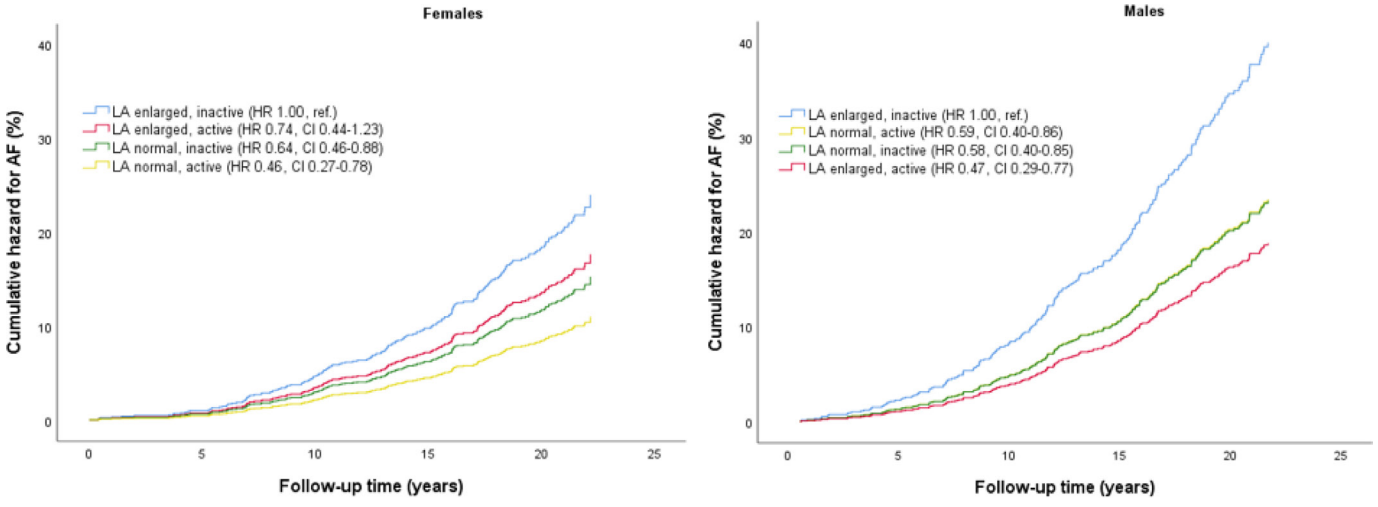

Figure 2 Adjusted cumulative hazard for AF by joint associations of PA and LA size with AF risk, stratified by sex. Differences between groups are indicated with HR and 95% CI. The model is adjusted for age, body mass index and systolic blood pressure. AF, atrial fibrillation, LA, left atrial/left atrium. The Tromsø Study 1994–1995.

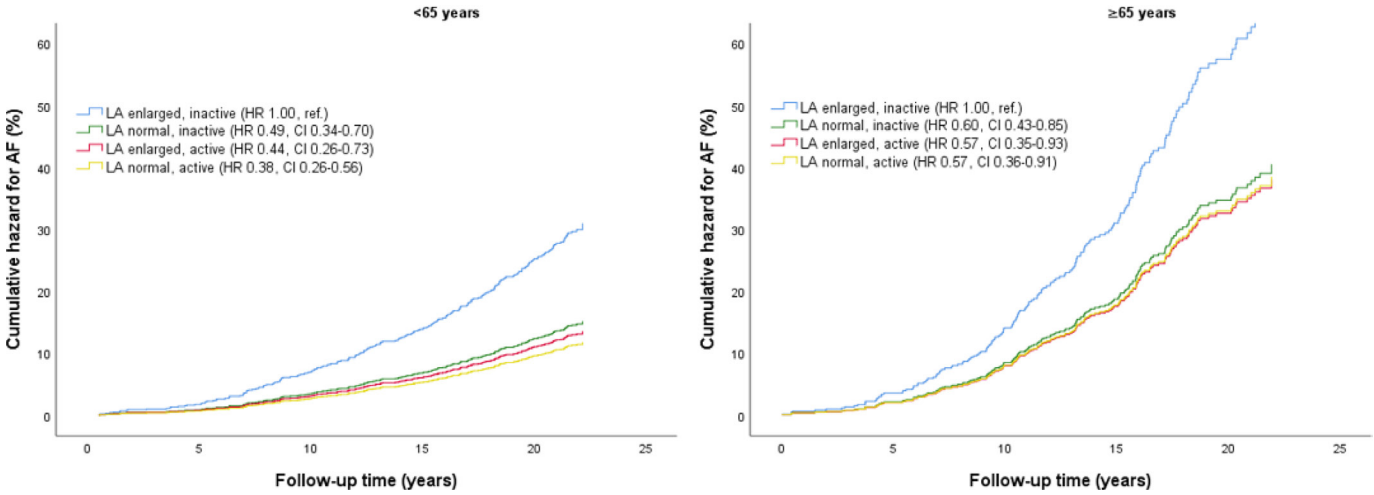

Figure 3 Adjusted cumulative hazard for AF by joint associations of PA and LA size with AF risk, stratified by age. Differences between groups are indicated with HR and 95% CI. The model is adjusted for sex, body mass index and systolic blood pressure. AF, atrial fibrillation, LA, left atrial/left atrium. The Tromsø Study 1994–1995.

DISCUSSION

To the best of our knowledge, this is the first study that has analysed both PA and LA size jointly as risk factors for AF in a general population. The main findings from our study are that PA was associated with lower risk of AF in a U-shaped pattern, and the increased AF risk with LA enlargement was attenuated by PA. Furthermore, the risk of AF in active participants with LA enlargement did not differ from active with normal LA size. These patterns were observed in both men and women, and in participants over/under 65 years.

Therefore, in our study of participants free from known cardiac pathology, LA enlargement does not represent increased risk of AF in physically active individuals. Furthermore, inclusion of several risk factors for AF in the analysis did not influence the associations between PA, LA size and AF.

Physical activity, LA size and AF

Overall, we observed 32% lower risk of AF in moderate active than in inactive participants, and a U-shaped association was seen between PA and risk of AF. The protective effect of PA on cardiovascular disease is well documented,[31] and several studies support our observation that moderate doses of PA reduces the risk of AF.[3 5 32] Also, our observation that the protective effect of PA on AF risk is offset by vigorous exercise, demonstrated by a U-shaped relationship, is consistent with previous studies.[5 6 33 34] Furthermore, increased risk of AF is seen in endurance athletes,[7 9 33] and with high levels of lifelong exercise.[8 34] Our results showed that active participants had similar AF risk regardless of LA size, suggesting that LA enlargement in active individuals free from known cardiac pathology is not associated with increased risk of AF.

To our knowledge, no previous studies have examined how the relationship between LA size and AF varies with PA, and if PA attenuates the risk of AF seen with LA enlargement, in the general population. Our results, that LA enlargement increases the risk of AF, are consistent with previous research in both the general population[10 11] and in healthy middle-aged individuals.[8] Furthermore, we observed that moderate PA attenuated the risk of AF in participants with LA enlargement, whereas PA did not attenuate the risk of AF in participants with normal LA size.

The higher risk of AF observed in inactive with LA enlargement may be due to pathological conditions elevating chronic LA pressure and volume overload,[12] for example, hypertension, LV diastolic dysfunction or heart failure, whereas the lower risk in active with LA enlargement may be due to the protective effect of moderate PA on modifiable cardiovascular risk factors.[35] In our study, the participants were free from known cardiac pathology, which may explain why there was no beneficial association between PA and AF in participants with normal LA size.

Atrial stretch in response to LA volume and pressure overload is a key stimulus for LA enlargement and may potentially induce release of factors leading to atrial myocyte hypertrophy, oxidative stress and fibrosis, which increases the risk of AF.[12 35] Although we excluded participants with known cardiac pathology at baseline, it is likely that the increased risk of AF in inactive with LA enlargement is explained by undetected pathological conditions we could not control for. Therefore, the reduced risk in active with LA enlargement may be the sum of the protective effect of moderate PA, outweighing the potentially increased risk of LA enlargement. However, the lower risk of AF in active with LA enlargement persisted even when we adjusted for multiple cardiovascular risk factors in our sensitivity analysis.

During vigorous exercise, atrial stretch may potentially release similar factors as in pathological conditions and thereby increase risk of AF,[12] but an important difference

between pathology and exercise is that the atrial pressure overload returns to normal when the exercise ceases.[12] However, when repeated over time, and with insufficient recovery between exercise bouts, this may contribute to the increased risk of AF observed with high amounts of cumulative lifetime moderate-to-vigorous PA or exercise.[8 34 35] Furthermore, it has been reported that male endurance athletes have a higher prevalence of masked hypertension (38%) than what is expected from the general population (8%–20%).[36] Thus, masked hypertension might also explain the increased risk of AF associated with exercise.[37] Other cardiac adaptations to vigorous exercise, associated with increased risk of AF, include increased vagal tone, resting bradycardia and electrical remodelling,[5 35] which all may reduce atrial refractory period and facilitate re-entry.[12]

Cardiac chamber enlargement is assumed to be a physiological and reversible adaptation to exercise training.[35] This adaptation is expressed as *the athlete's heart*[35] and is adapted to perfectly match the supply to the demands of exercise.[37] However, it is suggested that LA enlargement itself may be a substrate for AF in athletes,[19 35] and, therefore, that the athlete's heart may potentially be proarrhythmic independent of other abnormalities.[37]

Interestingly, the pathophysiology seems to differ between 'classical' AF and exercise-related AF. AF is usually associated with high age, comorbidities and other risk factors.[1] In contrast, people at risk of exercise-related AF are typically middle-aged men with athlete's heart and high amounts of cumulative lifetime exercise.[1 19] Moreover, this group typically has a lower prevalence of conventional risk factors for AF such as overweight and hypertension.[1] However, little is known about the long-term risk associated with exercise-related AF,[19] and longitudinal studies are needed to better understand the risk associated with exercise-related AF.

Age and sex in the association between PA, LA size and AF

It is well documented that increasing age is a prominent risk factor for AF, and that men have higher risk of AF than women.[1] In the Framingham Heart Study, the authors demonstrated a linear association between increasing age and risk of AF, and participants aged 60–69 years had fivefold risk of AF compared with participants aged 50–59.[38] Moreover, men had twofold incidence of AF compared with women.[38] Furthermore, the association between vigorous PA and AF differs between sexes, and higher risk of AF is seen in men, whereas women have lower risk of AF with high amounts of vigorous PA.[3 32 39]

In sex stratified analyses, we observed 79% higher risk of AF in men than in women, and when we stratified by age, participants ≥65 years had 2.6-fold higher risk of AF compared with participants <65 years. Furthermore, despite a higher overall risk of AF with LA enlargement, the risk of AF in active with LA enlargement was not higher in any sex, or age groups, compared with active participants with normal LA size.

Strengths and limitations

Our study has several strengths. First, the prospective design with a long follow-up period in combination with echocardiography data. Second, hospital-diagnosed AF confirmed by electrocardiography and validated by an independent expert endpoint committee. Third, the large number of participants, the high attendance and the large age span strengthen our generalisability to other Caucasian populations. Fourth, as the University Hospital of North Norway is the only hospital within a large geographical region, most hospital confirmed AF cases in our study population are likely uncovered. Finally, the broad diversity of covariates allowed us to adjust for multiple potential confounders.

Our study has limitations that should be addressed. First, LA size was assessed by M-mode anteroposterior LA diameter, which is less accurate and have more geometrically assumptions than the recommended biplane calculated LA volume.[26] However, a recent study demonstrated that anteroposterior LA diameter correlated well with LA volume (r=0.67), moreover, that there was high agreement (k=0.79) between LA volume and estimated LA volume by anteroposterior LA diameter in diagnosing LV diastolic dysfunction.[40] Second, self-reported PA is prone to both recall and social desirability bias,[41] although misclassification would probably have underestimated the true effects of PA. Third, as LA size was measured at baseline only, we cannot tell if the LA enlargement was due to exercise or pathology, or whether PA led to pathology and LA enlargement before baseline. However, the latter is less likely as we excluded all participants with present or previous known cardiac pathology, and we also adjusted for cardiovascular risk factors at baseline. Fourth, we cannot exclude residual confounding by measured or unmeasured variables (eg, masked hypertension, fibrosis or LA function). Finally, as AF was confirmed at the hospital, it is likely that some participants are misclassified as non-cases due to paroxysmal and/or silent AF that failed to be detected at examination. However, assuming that this misclassification is non-differential, the true AF prevalence may be higher than in our study, and the association between PA and AF is probably underestimated.

In conclusion, our prospective study of participants free from known cardiac pathology suggests a U-shaped relationship between PA and AF. Moderate PA was associated with reduced risk of AF, whereas vigorous PA attenuated the protective effect of moderate PA. Moreover, PA attenuated the increased AF risk with LA enlargement in both men and women, and in participants over/under 65 years. We suggest that the protective effect of moderate PA outweighs the potential risk of AF with LA enlargement. Further research is warranted to clarify the association between LA enlargement and AF in relation to PA, preferably assessed with biplane-derived LA volume and objective measures of PA.

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Appendices

Appendix A: List of links to invitations, information brochures, and consent forms for Tromsø4, Tromsø6 and Tromsø7

Appendix B: Questionnaires, Tromsø4

Appendix C: Questionnaire, Tromsø6

Appendix D: Questionnaire, Tromsø7

Appendix E: Approval from the Regional Committee for Medical and Health Research Ethics

Appendix A

List of links to information brochures and consent forms for Tromsø4, Tromsø6 and Tromsø7

Tromsø4 (1994-95)

- Invitation brochure: https://uit.no/Content/710329/cache=20203011111556/Troms%C3%B8_IV_brosjyre.pdf
- Consent form: https://uit.no/Content/710357/cache=20203011130444/samtykkerklaering.tromso4.pdf

Tromsø6 (2007-08)

- Invitation brochure: https://uit.no/Content/100340/Forespoersel_om_deltakelse_t6.pdf
- Consent form: https://uit.no/Content/111929/Samtykke Tr6.pdf

Tromsø7 (2015-16)

- Invitation brochure: https://uit.no/Content/710341/cache=20203011123325/brosjyre.troms%C3%B87.pdf
- Consent form: https://uit.no/Content/575211/cache=20180805144729/Samtykke.den7.Tromsoundersokelsen.pdf

Appendix B

Questionnaires, Tromsø4

Innbydelse til

HELSEUNDERSØKELSEN

Fødselsdato	Personnr.	Kommune	Kretsnr.

Velkommen til helseundersøkelsen i Tromsø!

Helseundersøkelsen kommer nå til Tromsø. Tid og sted for frammøte finner du nedenfor. Du finner også en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber deg fylle ut spørreskjemaet på baksiden og ta det med til undersøkelsen.

Undersøkelsen blir mest verdifull om frammøtet blir så fullstendig som mulig. Vi håper derfor at du har mulighet til å komme. Møt selv om du kjenner deg frisk, om du er under legebehandling, eller om du har fått målt kolesterol og blodtrykk i den senere tid.

Vennlig hilsen
Kommunehelsetjenesten
Fagområdet medisin, Universitetet i Tromsø
Statens helseundersøkelser

EGEN HELSE

Hvordan er helsen din nå? *Sett bare ett kryss.*

Dårlig	12	1
Ikke helt god		2
God		3
Svært god		4

Har du, eller har du hatt:

	JA	NEI	Alder første gang
Hjerteinfarkt 13			år
Angina pectoris (hjertekrampe) 16			år
Hjerneslag/hjerneblødning 19			år
Astma 22			år
Diabetes (sukkersyke) 25			år

Bruker du medisin mot høyt blodtrykk?

Nå	28	1
Før, men ikke nå		2
Aldri brukt		3

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 29 — JA / NEI

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig? 30				
Plaget av angst? 31				
Trygg og rolig? 32				
Irritabel? 33				
Glad og optimistisk? 34				
Nedfor/deprimert? 35				
Ensom? 36				
	1	2	3	4

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 37 — JA / NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 38 — JA / NEI

Hvis "JA", hvor mange år tilsammen? 39 — Antall år

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? 41 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig? 43		
Sigarer/sigarillos daglig? 44		
Pipe daglig? 45		

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 46 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 48 — Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 52 — Alder år

Hvor mange år tilsammen har du røykt daglig? 54 — Antall år

MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*
Arbeidsvei regnes som fritid.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* 56				
Hard fysisk aktivitet *(svett/andpusten)* 57				
	1	2	3	4

KAFFE

Hvor mange kopper kaffe drikker du daglig?
Sett 0 hvis du ikke drikker kaffe daglig.

Kokekaffe	58	Antall kopper
Annen kaffe	60	Antall kopper

ALKOHOL

Er du total avholdsmann/-kvinne? 62 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. 63 — Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker? 65
Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol.

Øl	Vin	Brennevin
glass	glass	glass

FETT

Hva slags margarin eller smør bruker du vanligvis på brødet? *Sett ett kryss.*

Bruker ikke smør/margarin	71	1
Meierismør		2
Hard margarin		3
Bløt (soft) margarin		4
Smør/margarin blanding		5
Lettmargarin		6

UTDANNING/ARBEID

Hvilken utdanning er den høyeste du har fullført?

Grunnskole, 7-10 år, framhaldsskole, folkehøgskole	72	1
Realskole, middelskole, yrkesskole, 1-2-årig videregående skole		2
Artium, øk.gymnas, allmennfaglig retning i videregående skole		3
Høgskole/universitet, mindre enn 4 år		4
Høgskole/universitet, 4 år eller mer		5

Hva slags arbeidssituasjon har du nå?

Lønnet arbeid	73	
Heltids husarbeid	74	
Utdanning, militærtjeneste	75	
Arbeidsledig, permittert	76	

Hvor mange timer lønnet arbeid har du i uka? 77 — Antall timer

Mottar du nå noen av følgende ytelser?

Syketrygd (sykmeldt)	79	
Attføring	80	
Uførepensjon	81	
Alderspensjon	82	
Sosialstøtte	83	
Arbeidsløshetstrygd	84	

SYKDOM I FAMILIEN

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 85 — JA / NEI / VET IKKE

Helseundersøkelsen i Tromsø

Hovedformålet med Tromsøundersøkelsene er å skaffe ny kunnskap om hjerte-karsykdommer for å kunne forebygge dem. I tillegg skal undersøkelsen øke kunnskapen om kreftsykdommer og andre alminnelige plager som f.eks. allergier, smerter i muskulatur og nervøse lidelser. Vi ber deg derfor svare på noen spørsmål om forhold som kan ha betydning for risikoen for disse og andre sykdommer.

Skjemaet er en del av Helseundersøkelsen som er godkjent av Datatilsynet og av Regional komite for medisinsk forskningsetikk. Svarene brukes bare til forskning og behandles strengt fortrolig. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

Hvis du er i tvil om hva du skal svare, sett kryss i den ruten som du synes passer best.

Det utfylte skjema sendes i vedlagte svarkonvolutt. Portoen er betalt.

På forhånd takk for hjelpen!

Med vennlig hilsen

Fagområdet medisin
Universitetet i Tromsø **Statens helseundersøkelser**

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss i ruten under og returner skjemaet. Da slipper du purring.

Jeg ønsker ikke å besvare spørreskjemaet ..... 17 ❑

Dag Mnd År

Dato for utfylling av skjema: ..... 18 ...../...../.....

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?

..... 24 - 28

Hvis du ikke bodde i Norge, oppgi land i stedet for kommune.

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ..... 29 ❑
- Gode ..... ❑
- Vanskelige ..... ❑
- Meget vanskelige ..... ❑

Hvor mange av de første 3 årene av ditt liv
- bodde du i by? ..... 30 _____ år
- hadde dere katt eller hund i hjemmet? ..... 31 _____ år

Hvor mange av de første 15 årene av ditt liv
- bodde du i by? ..... 32 _____ år
- hadde dere katt eller hund i hjemmet? ..... 34 _____ år

BOLIG

Hvem bor du sammen med?

Sett ett kryss for hvert spørsmål og angi antall.		Ja	Nei	Antall
Ektefelle/samboer	36	❑	❑	
Andre personer over 18 år	37	❑	❑	_____
Personer under 18 år	40	❑	❑	_____

Hvor mange av barna har plass i barnehage? ..... 43 _____

Hvilken type bolig bor du i?
- Enebolig/villa ..... 45 ❑ 1
- Gårdsbruk ..... ❑ 2
- Blokk/terrasseleilighet ..... ❑ 3
- Rekkehus/2-4 mannsbolig ..... ❑ 4
- Annen bolig ..... ❑ 5

Hvor stor er din boenhet? ..... 46 _____ m^2

I omtrent hvilket år ble boligen bygget? ..... 49 _____

		Ja	Nei
Er boligen isolert etter 1970?	53	❑	❑
Bor du i underetasje/kjeller?	54	❑	❑
Hvis "Ja", er gulvbelegget lagt på betong?	55	❑	❑

Hvordan er boligen hovedsakelig oppvarmet?
- Elektrisk oppvarming ..... 56 ❑
- Vedfyring ..... ❑
- Sentralvarmeanlegg oppvarmet med:
  - Parafin ..... ❑
  - Elektrisitet ..... ❑

		Ja	Nei
Er det heldekkende tepper i stua?	60	❑	❑
Er det katt i boligen?	61	❑	❑
Er det hund i boligen?	62	❑	❑

ARBEID

Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive ditt arbeid?
- For det meste stillesittende arbeid? ..... 63 ❑ 1
  (f.eks. skrivebordsarbeid, montering)
- Arbeid som krever at du går mye? ..... ❑ 2
  (f.eks. ekspeditørarb., lett industriarb., undervisning)
- Arbeid hvor du går og løfter mye? ..... ❑ 3
  (f.eks. postbud, pleier, bygningsarbeid)
- Tungt kroppsarbeid? ..... ❑ 4
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygn.arb.)

Kan du selv bestemme hvordan arbeidet ditt skal legges opp?
- Nei, ikke i det hele tatt ..... 64 ❑ 1
- I liten grad ..... ❑ 2
- Ja, i stor grad ..... ❑ 3
- Ja, det bestemmer jeg selv ..... ❑ 4

		Ja	Nei
Har du skiftarbeid, nattarbeid eller går vakter?	65	❑	❑

Har du noen av følgende yrker (heltid eller deltid)?

Sett ett kryss for hvert spørsmål.		Ja	Nei
Sjåfør	66	❑	❑
Bonde/gårdbruker		❑	❑
Fisker		❑	❑

EGNE SYKDOMMER

Har du noen gang hatt:
Sett ett kryss for hvert spørsmål. Oppgi alderen ved hendelsen.
*Hvis det har skjedd flere ganger, hvor gammel var du **siste** gang?*

	Ja	Nei	Alder
Lårhalsbrudd 69	❑	❑	_____
Brudd ved håndledd/underarm 72	❑	❑	_____
Nakkesleng (whiplash) 75	❑	❑	_____
Skade som førte til sykehusinnleggelse 78	❑	❑	_____
Sår på magesekken 81	❑	❑	_____
Sår på tolvfingertarmen 84	❑	❑	_____
Magesår-operasjon 87	❑	❑	_____
Operasjon på halsen 90	❑	❑	_____

Har du eller har du hatt:
Sett ett kryss for hvert spørsmål.

	Ja	Nei
Kreftsykdom 93	❑	❑
Epilepsi (fallesyke)	❑	❑
Migrene	❑	❑
Kronisk bronkitt	❑	❑
Psoriasis	❑	❑
Benskjørhet (osteoporose) 98	❑	❑
Fibromyalgi/fibrositt/kronisk smertesyndrom	❑	❑
Psykiske plager som du har søkt hjelp for	❑	❑
Stoffskiftesykdom (skjoldbruskkjertel)	❑	❑
Sykdom i leveren	❑	❑
Nyrestein 103	❑	❑
Blindtarmsoperasjon	❑	❑
Allergi og overfølsomhet		
Atopisk eksem (f.eks. barneeksem)	❑	❑
Håndeksem	❑	❑
Høysnue	❑	❑
Matvareallergi 108	❑	❑
Annen overfølsomhet (ikke allergi)	❑	❑

Hvor mange ganger har du hatt forkjølelse, influensa, "ræksjuka" og lignende siste halvår? ..110 ____ ganger

	Ja	Nei
Har du hatt dette siste 14 dager? 112	❑	❑

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene:
Kryss av for "Ingen" hvis ingen av slektningene har hatt sykdommen.

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 113	❑	❑	❑	❑	❑	❑
Hjerteinfarkt før 60 års alder 119	❑	❑	❑	❑	❑	❑
Kreftsykdom 125	❑	❑	❑	❑	❑	❑
Astma 131	❑	❑	❑	❑	❑	❑
Mage/tolvfingertarm-sår 137	❑	❑	❑	❑	❑	❑
Benskjørhet (osteoporose) 143	❑	❑	❑	❑	❑	❑
Psykiske plager 149	❑	❑	❑	❑	❑	❑
Allergi 155	❑	❑	❑	❑	❑	❑
Diabetes (sukkersyke) 161	❑	❑	❑	❑	❑	❑
– alder da de fikk diabetes 167	____	____	____	____	____	____

SYMPTOMER

	Ja	Nei
Hoster du omtrent daglig i perioder av året? 177	❑	❑
Hvis "Ja":		
Er hosten vanligvis ledsaget av oppspytt? 178	❑	❑
Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste år? 179	❑	❑
Har du hatt episoder med piping i brystet? 180	❑	❑
Hvis "Ja", har dette oppstått:		
Sett ett kryss for hvert spørsmål.		
Om natten 181	❑	❑
Ved luftveisinfeksjoner	❑	❑
Ved fysiske anstrengelser	❑	❑
Ved sterk kulde	❑	❑
Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste år? 185	❑	❑

Hvor ofte er du plaget av søvnløshet?

Aldri, eller noen få ganger i året 186	❑ 1
1-2 ganger i måneden	❑ 2
Omtrent en gang i uken	❑ 3
Mer enn en gang i uken	❑ 4

Hvis du er plaget av søvnløshet i perioder, når på året er du mest plaget?

Ingen spesiell tid 187	❑ 1
Særlig i mørketiden	❑ 2
Særlig i midnattsoltiden	❑ 3
Særlig vår og høst	❑ 4

	Ja	Nei
Har du det siste året vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 188	❑	❑

Hvor ofte er du plaget av hodepine?

Sjelden eller aldri 189	❑ 1
En eller flere ganger i måneden	❑ 2
En eller flere ganger i uken	❑ 3
Daglig	❑ 4

Hender det at tanken på å få alvorlig sykdom bekymrer deg?

Ikke i det hele tatt 190	❑ 1
Bare i liten grad	❑ 2
En del	❑ 3
Ganske mye	❑ 4

BRUK AV HELSEVESENET

Hvor mange ganger har du siste året, på grunn av egen helse eller sykdom, vært:
*Sett **0** hvis du **ikke** har hatt slik kontakt.*

	Antall ganger siste år
Hos vanlig lege/legevakt 191	_____
Hos psykolog eller psykiater	_____
Hos annen legespesialist utenfor sykehus	_____
På poliklinikk 197	_____
Innlagt i sykehus	_____
Hos bedriftslege	_____
Hos fysioterapeut 203	_____
Hos kiropraktor	_____
Hos akupunktør	_____
Hos tannlege 209	_____
Hos naturmedisiner (homøopat, soneterapeut o.l.)	_____
Hos håndspålegger, synsk eller "leser"	_____

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig? Angi hvor mange måneder du brukte dem.
*Sett **0** hvis du **ikke** har brukt midlene.*

Legemidler
- Smertestillende ....215 _____ mnd.
- Sovemedisin .... _____ mnd.
- Beroligende midler .... _____ mnd.
- Medisin mot depresjon ....221 _____ mnd.
- Allergimedisin .... _____ mnd.
- Astmamedisin .... _____ mnd.

Kosttilskudd
- Jerntabletter ....227 _____ mnd.
- Kalktabletter eller benmel .... _____ mnd.
- Vitamin D-tilskudd .... _____ mnd.
- Andre vitamintilskudd ....233 _____ mnd.
- Tran eller fiskeoljekapsler .... _____ mnd.

Har du de siste 14 dager brukt følgende legemidler eller kosttilskudd?
*Sett **ett** kryss for **hvert** spørsmål.*

	Ja	Nei
Legemidler		
Smertestillende medisin 237	❑	❑
Febersenkende medisin	❑	❑
Migrenemedisin	❑	❑
Eksemsalve	❑	❑
Hjertemedisin (ikke blodtrykksmedisin)	❑	❑
Kolesterolsenkende medisin 242	❑	❑
Sovemedisin	❑	❑
Beroligende medisin	❑	❑
Medisin mot depresjon	❑	❑
Annen nervemedisin	❑	❑
Syrenøytraliserende midler 247	❑	❑
Magesårsmedisin	❑	❑
Insulin	❑	❑
Tabletter mot diabetes (sukkersyke)	❑	❑
Tabletter mot lavt stoffskifte (thyroxin)	❑	❑
Kortisontabletter 252	❑	❑
Annen medisin	❑	❑
Kosttilskudd		
Jerntabletter	❑	❑
Kalktabletter eller benmel	❑	❑
Vitamin D-tilskudd	❑	❑
Andre vitamintilskudd 257	❑	❑
Tran eller fiskeoljekapsler	❑	❑

VENNER

Hvor mange gode venner har du som du kan snakke fortrolig med og gi deg hjelp når du trenger det? ....259 ____ gode venner
Tell ikke med de du bor sammen med, men ta med andre slektninger!

Hvor mange av disse gode vennene har du kontakt med minst en gang i måneden? ....261 ____

	Ja	Nei
Føler du at du har nok gode venner? 263	❑	❑

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?
- Aldri, eller noen få ganger i året ....264 ❑ 1
- 1-2 ganger i måneden .... ❑ 2
- Omtrent en gang i uken .... ❑ 3
- Mer enn en gang i uken .... ❑ 4

KOSTVANER

Hvis du bruker smør eller margarin på brødet, hvor mange skiver rekker en liten porsjonspakning vanligvis til? Vi tenker på slik porsjonspakning som du får på fly, på kafé o.l. (10-12 gram).

Den rekker til omtrent ....265 _____ skiver

Hva slags fett blir vanligvis brukt til **matlaging** (ikke på brødet) i din husholdning?
- Meierismør ....266 ❑
- Hard margarin .... ❑
- Bløt (Soft) margarin .... ❑
- Smør/margarin blanding .... ❑
- Oljer ....270 ❑

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis?
Sett ett eller to kryss!

	Loff	Fint brød	Kneip-brød	Grov-brød	Knekke-brød
Brødtypen ligner mest på:	❑ 271	❑	❑	❑	❑ 275

Hvor mye (i **antall** glass, kopper, poteter eller brødskiver) spiser eller drikker du vanligvis **daglig** av følgende matvarer?
*Kryss av for **alle** matvarene.*

	0	Færre enn 1	1-2	3-4	5-6	Mer enn 6
Helmelk (søt eller sur) (glass) 276	❑	❑	❑	❑	❑	❑
Lettmelk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Skummet melk (søt eller sur) (glass)	❑	❑	❑	❑	❑	❑
Te (kopper)	❑	❑	❑	❑	❑	❑
Appelsinjuice (glass)	❑	❑	❑	❑	❑	❑
Poteter 281	❑	❑	❑	❑	❑	❑
Brødskiver totalt (inkl. knekkebrød)	❑	❑	❑	❑	❑	❑
Brødskiver med						
– fiskepålegg (f.eks. makrell i tomat)	❑	❑	❑	❑	❑	❑
– magert kjøttpålegg (f.eks. skinke)	❑	❑	❑	❑	❑	❑
– fetere kjøttpålegg (f.eks. salami)	❑	❑	❑	❑	❑	❑
– gulost 286	❑	❑	❑	❑	❑	❑
– brunost	❑	❑	❑	❑	❑	❑
– kaviar	❑	❑	❑	❑	❑	❑
– syltetøy og annet søtt pålegg	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Hvor mange **ganger i uka** spiser du vanligvis følgende matvarer?
*Kryss av for **alle** matvarene.*

	Aldri	Færre enn 1	1	2-3	4-5	Omtrent daglig
Yoghurt 290	❑	❑	❑	❑	❑	❑
Kokt eller stekt egg	❑	❑	❑	❑	❑	❑
Frokostblanding/havregryn o.l.	❑	❑	❑	❑	❑	❑
Middag med						
– rent kjøtt	❑	❑	❑	❑	❑	❑
– pølser/kjøttpudding/-kaker	❑	❑	❑	❑	❑	❑
– feit fisk (f.eks. laks/uer) 295	❑	❑	❑	❑	❑	❑
– mager fisk (f.eks. torsk)	❑	❑	❑	❑	❑	❑
– fiskeboller/-pudding/-kaker	❑	❑	❑	❑	❑	❑
– grønnsaker	❑	❑	❑	❑	❑	❑
Majones, remulade o.l.	❑	❑	❑	❑	❑	❑
Gulrøtter 300	❑	❑	❑	❑	❑	❑
Blomkål/kål/brokkoli	❑	❑	❑	❑	❑	❑
Epler/pærer	❑	❑	❑	❑	❑	❑
Appelsiner, mandariner o.l.	❑	❑	❑	❑	❑	❑
Sukkerholdige leskedrikker	❑	❑	❑	❑	❑	❑
Sukkerfrie («Light») leskedrikker	❑	❑	❑	❑	❑	❑
Sjokolade	❑	❑	❑	❑	❑	❑
Vafler, kaker o.l. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALKOHOL

Hvor ofte pleier du å drikke	øl?	vin?	brennevin?
Aldri, eller noen få ganger i året	❑ 308	❑	❑ 1
1-2 ganger i måneden	❑	❑	❑ 2
Omtrent 1 gang i uken	❑	❑	❑ 3
2-3 ganger i uken	❑	❑	❑ 4
Omtrent hver dag	❑	❑	❑ 5 310

Omtrent hvor ofte har du i løpet av siste år drukket alkohol tilsvarende minst 5 halvflasker øl, en helflaske vin eller 1/4 flaske brennevin?

- Ikke siste år ..... 311 ❑ 1
- Noen få ganger ..... ❑ 2
- 1 - 2 ganger per måned ..... ❑ 3
- 1 - 2 ganger i uken ..... ❑ 4
- 3 eller flere ganger i uken ..... ❑ 5

I omtrent hvor mange år har ditt alkoholforbruk vært slik du har svart i spørsmålene over? ..... 312 _____ år

SLANKING

Omtrent hvor mange ganger har du bevisst prøvd å slanke deg? Sett **0** hvis ingen forsøk.

- – før 20 år ..... 314 _____ ganger
- – senere ..... 316 _____ ganger

Hvis du har slanket deg, omtrent hvor mange kilo har du på det meste gått ned i vekt?

- – før 20 år ..... 318 _____ kg
- – senere ..... 320 _____ kg

Hvilken vekt ville du være tilfreds med (din "trivselsvekt")? ..... 322 _____ kg

UFRIVILLIG URINLEKKASJE

Hvor ofte har du ufrivillig urinlekkasje?

- Aldri ..... 325 ❑ 1
- Ikke mer enn en gang i måneden ..... ❑ 2
- To eller flere ganger i måneden ..... ❑ 3
- Ukentlig eller oftere ..... ❑ 4

Dine kommentarer:

BESVARES BARE AV KVINNER

MENSTRUASJON

Hvor gammel var du da du fikk menstruasjon første gang? ..... 326 _____ år

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... 328 _____ år

Når du ser bort fra svangerskap og barselsperiode, har du noen gang vært blødningsfri i minst 6 måneder? 330	Ja ❑	Nei ❑

Hvis "Ja", hvor mange ganger? ..... 331 _____ ganger

Hvis du fremdeles har menstruasjon eller er gravid:

Hvilken dato startet din siste menstruasjon? ..... 333 dag/ mnd/ år ___/___/___

Bruker du vanligvis smertestillende legemidler for å dempe menstruasjonsplager? 339	Ja ❑	Nei ❑

SVANGERSKAP

Hvor mange barn har du født? ..... 340 _____ barn

Er du gravid nå? 342	Ja ❑	Nei ❑	Usikker ❑

Har du i forbindelse med svangerskap hatt for høyt blodtrykk og/eller eggehvite (protein) i urinen? 343	Ja ❑	Nei ❑

Hvis "Ja", i hvilket svangerskap?

	Svangerskap Første	Senere
For høyt blodtrykk 344	❑	❑
Eggehvite i urinen 346	❑	❑

Hvis du har født, fyll ut for hvert barn barnets fødselsår og omtrent antall måneder du ammet barnet.

Barn:	Fødselsår:	Antall måneder med amming:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

PREVENSJON OG ØSTROGEN

Bruker du, eller har du brukt:	Nå	Før	Aldri
P-pille (også minipille) 372	❑	❑	❑
Hormonspiral	❑	❑	❑
Østrogen (tabletter eller plaster) 374	❑	❑	❑
Østrogen (krem eller stikkpiller)	❑ 1	❑ 2	❑ 3

Hvis du bruker p-pille, hormonspiral eller østrogen; hvilket merke bruker du nå?

376 .....

Hvis du bruker eller har brukt p-pille:

Alder da du begynte med P-piller? ..... 380 _____ år

Hvor mange år har du tilsammen brukt P-piller? ..... 382 _____ år

Dersom du har født, hvor mange år brukte du P-piller før første fødsel? ..... 384 _____ år

Hvis du har sluttet å bruke P-piller:

Alder da du sluttet? ..... 386 _____ år

Takk for hjelpen! Husk å postlegge skjemaet idag!

Helseundersøkelsen i Tromsø

Appendix C

Questionnaire, Tromsø6

Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 **Hvordan vurderer du din egen helse sånn i alminnelighet?**

- ☐ Meget god
- ☐ God
- ☐ Verken god eller dårlig
- ☐ Dårlig
- ☐ Meget dårlig

2 **Hvordan synes du at helsen din er sammenlignet med andre på din alder?**

- ☐ Mye bedre
- ☐ Litt bedre
- ☐ Omtrent lik
- ☐ Litt dårligere
- ☐ Mye dårligere

3 **Har du eller har du hatt?**

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐	☐	
Angina pectoris *(hjertekrampe)*	☐	☐	
Hjerneslag/hjerneblødning	☐	☐	
Hjerteflimmer *(atrieflimmer)*	☐	☐	
Høyt blodtrykk	☐	☐	
Beinskjørhet *(osteoporose)*	☐	☐	
Astma	☐	☐	
Kronisk bronkitt/emfysem/KOLS	☐	☐	
Diabetes	☐	☐	
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	
Lavt stoffskifte	☐	☐	
Nyresykdom, unntatt urinveisinfeksjon	☐	☐	
Migrene	☐	☐	

4 **Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?**

☐ Ja ☐ Nei

5 **Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?**

- ☐ Aldri, eller noen få ganger
- ☐ 1-3 ganger i måneden
- ☐ Omtrent 1 gang i uken
- ☐ Mer enn 1 gang i uken

6 **Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?** (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐

BRUK AV HELSETJENESTER

7 **Har du i løpet av de siste 12 måneder vært hos:** Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege	☐	☐	
Psykiater/psykolog	☐	☐	
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	
Fysioterapeut	☐	☐	
Kiropraktor	☐	☐	
Annen behandler *(homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l)*	☐	☐	
Tannlege/tannpleier	☐	☐	

8 **Har du i løpet av de siste 12 måneder vært på sykehus?**

	Ja	Nei	Ant ggr
Innlagt på sykehus	☐	☐	
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk	☐	☐	
Ved annen sykehuspoliklinikk	☐	☐	

9 **Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?**

☐ Ja ☐ Nei

BRUK AV MEDISINER

10 **Bruker du, eller har du brukt, noen av følgende medisiner?** (Sett ett kryss for hver linje)

	Aldri brukt	Nå	Før	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Medisin mot hjertesykdom	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Medisin mot beinskjørhet *(osteoporose)*	☐	☐	☐	
Insulin	☐	☐	☐	
Diabetesmedisin *(tabletter)*	☐	☐	☐	
Stoffskiftemedisinene Thyroxin/levaxin	☐	☐	☐	

11 **Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?** (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende reseptfrie	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

12 **Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode.** (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

13 **Hvem bor du sammen med?** (Sett kryss for hvert spørsmål og angi antall)

	Ja	Nei	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

14 **Kryss av for de slektninger som har eller har hatt**

	Foreldre	Barn	Søsken
Hjerteinfarkt	☐	☐	☐
Hjerteinfarkt før fylte 60 år	☐	☐	☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐
Hjerneslag/hjerneblødning	☐	☐	☐
Beinskjørhet *(osteoporose)*	☐	☐	☐
Magesår/tolvfingertarmsår	☐	☐	☐
Astma	☐	☐	☐
Diabetes	☐	☐	☐
Demens	☐	☐	☐
Psykiske plager	☐	☐	☐
Rusproblemer	☐	☐	☐

15 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

16 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

17 **Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?**

☐ Aldri, eller noen få ganger i året
☐ 1-2 ganger i måneden
☐ Omtrent 1 gang i uken
☐ Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

18 **Hva er din høyeste fullførte utdanning?** (Sett ett kryss)

☐ Grunnskole, framhaldsskole eller folkehøyskole
☐ Yrkesfaglig videregående, yrkesskole eller realskole
☐ Allmennfaglig videregående skole eller gymnas
☐ Høyskole eller universitet, mindre enn 4 år
☐ Høyskole eller universitet, 4 år eller mer

19 **Hva er din hovedaktivitet?** (Sett ett kryss)

☐ Yrkesaktiv heltid
☐ Yrkesaktiv deltid
☐ Arbeidsledig
☐ Hjemmeværende
☐ Pensjonist/trygdet
☐ Student/militærtjeneste

20 **Mottar du noen av følgende ytelser?**

- ☐ Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
- ☐ Sykepenger (er sykemeldt)
- ☐ Rehabiliterings-/attføringspenger
- ☐ Uføreytelse/pensjon, hel
- ☐ Uføreytelse/pensjon, delvis
- ☐ Dagpenger under arbeidsledighet
- ☐ Overgangstønad
- ☐ Sosialhjelp/-stønad

21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.

- ☐ Under 125 000 kr
- ☐ 125 000-200 000 kr
- ☐ 201 000-300 000 kr
- ☐ 301 000-400 000 kr
- ☐ 401 000-550 000 kr
- ☐ 551 000-700 000 kr
- ☐ 701 000 -850 000 kr
- ☐ Over 850 000 kr

22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**

- ☐ Ja
- ☐ Nei

FYSISK AKTIVITET

23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks postbud, pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

24 **Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.** (Sett kryss i den ruta som passer best)

- ☐ Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
- ☐ Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka

25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uken
- ☐ En gang i uken
- ☐ 2-3 ganger i uken
- ☐ omtrent hver dag

26 **Hvor hardt mosjonerer du da i gjennomsnitt?**

- ☐ Tar det rolig uten å bli andpusten eller svett.
- ☐ Tar det så hardt at jeg blir andpusten og svett
- ☐ Tar meg nesten helt ut

27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**

- ☐ Mindre enn 15 minutter
- ☐ 15-29 minutter
- ☐ 30 minutter – 1 time
- ☐ Mer enn 1 time

ALKOHOL OG TOBAKK

28 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2-4 ganger hver måned
- ☐ 2-3 ganger pr. uke
- ☐ 4 eller flere ganger pr.uke

29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**

- ☐ 1-2
- ☐ 3-4
- ☐ 5-6
- ☐ 7-9
- ☐ 10 eller flere

30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ aldri
- ☐ sjeldnere enn månedlig
- ☐ månedlig
- ☐ ukentlig
- ☐ daglig eller nesten daglig

31 **Røyker du av og til, men ikke daglig?**

- ☐ Ja
- ☐ Nei

32 **Har du røykt/røyker du daglig?**

- ☐ Ja, nå
- ☐ Ja, tidligere
- ☐ Aldri

33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**

Antall år ☐☐

34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**

Antall sigaretter ☐☐

35 **Hvor gammel var du da du begynte å røyke daglig?**

Antall år ☐☐

36 **Hvor mange år til sammen har du røykt daglig?**

Antall år ☐☐

37 **Bruker du, eller har du brukt, snus eller skrå?**

- ☐ Nei, aldri
- ☐ Ja, men jeg har sluttet
- ☐ Ja, av og til
- ☐ Ja, daglig

KOSTHOLD

38 **Spiser du vanligvis frokost hver dag?**

☐ Ja ☐ Nei

39 **Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag?** (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter ☐☐

40 **Hvor mange ganger i uken spiser du varm middag?**

Antall ☐☐

41 **Hvor ofte spiser du vanligvis disse matvarene?**
(Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Kjøtt *(ikke kvernet)*	☐	☐	☐	☐	☐
Kvernet kjøtt *(pølser, hamburger o.l)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk	☐	☐	☐	☐	☐
Feit fisk *(f.eks.laks, ørret, makrell, sild, kveite,uer)*	☐	☐	☐	☐	☐

42 **Hvor mye drikker du vanligvis av følgende?**
(Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker med sukker	☐	☐	☐	☐	☐

43 **Hvor mange kopper kaffe og te drikker du daglig?**
(sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe	☐☐
Kokekaffe/presskanne	☐☐
Annen kaffe	☐☐
Te	☐☐

44 **Hvor ofte spiser du vanligvis fiskelever?**
(For eksempel i mølje)

☐ Sjelden/aldri ☐ 1-3 g i året ☐ 4-6 g i året
☐ 7-12 g i året ☐ Oftere

45 **Bruker du følgende kosttilskudd?**

	Daglig	Iblant	Nei
Tran, trankapsler	☐	☐	☐
Omega 3 kapsler *(fiskeolje,selolje)*	☐	☐	☐
Kalktabletter	☐	☐	☐

SPØRSMÅL TIL KVINNER

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Usikker

47 **Hvor mange barn har du født?**

Antall ☐☐

48 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.**
(Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	☐☐☐☐	☐☐☐☐	☐☐
2	☐☐☐☐	☐☐☐☐	☐☐
3	☐☐☐☐	☐☐☐☐	☐☐
4	☐☐☐☐	☐☐☐☐	☐☐
5	☐☐☐☐	☐☐☐☐	☐☐
6	☐☐☐☐	☐☐☐☐	☐☐

49 **Har du i forbindelse med svangerskap hatt for høyt blodtrykk?**

☐ Ja ☐ Nei

50 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

51 **Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?**

☐ Ja ☐ Nei

52 **Hvis Ja, i hvilket svangerskap?**

☐ Første ☐ Senere

53 **Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?**

☐ Ja ☐ Nei

54 **Hvis Ja, hvilke(t) barn**

Barn 1	Barn 2	Barn 3	Barn 4	Barn 5	Barn 6
☐	☐	☐	☐	☐	☐

55 **Hvor gammel var du da du fikk menstruasjon første gang?**

Antall år ☐☐

56 **Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?**

P-pille, hormonspiral eller lignende ☐ Ja ☐ Nei
Hormonpreparat for overgangs-alderen ☐ Ja ☐ Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

LUNDBLAD MEDIA AS, TROMSØ, 77 75 32 50 - ONR 082222

Appendix D

Questionnaire, Tromsø7

Tromsø-undersøkelsen
2015–2016

KONFIDENSIELT

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Bruk blokkbokstaver. Du kan ikke bruke komma.

Dato for utfylling: ☐☐☐☐☐☐

HELSE OG SYKDOMMER

1.1 Hvordan vurderer du din egen helse sånn i alminnelighet?

Meget god	God	Verken god eller dårlig	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

1.2 Hvordan synes du at helsen din er sammenlignet med andre på din alder?

Mye bedre	Litt bedre	Omtrent lik	Litt dårligere	Mye dårligere
☐	☐	☐	☐	☐

1.3 Har du eller har du hatt?
Sett ett kryss per linje.

	Nei	Ja nå	Før, ikke nå	Alder første gang
Høyt blodtrykk	☐	☐	☐	☐☐
Hjerteinfarkt	☐		☐	☐☐
Hjertesvikt	☐	☐	☐	☐☐
Atrieflimmer *(hjerteflimmer)*	☐	☐	☐	☐☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐	☐☐
Hjerneslag/hjerneblødning	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Nyresykdom *(unntatt urinveisinfeksjon)*	☐	☐	☐	☐☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐	☐☐
Astma	☐	☐	☐	☐☐
Kreft	☐	☐	☐	☐☐
Revmatoid artritt *(leddgikt)*	☐	☐	☐	☐☐
Artrose *(slitasjegikt)*	☐	☐	☐	☐☐
Migrene	☐	☐	☐	☐☐
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	☐	☐☐

1.4 Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

☐ Nei ☐ Ja

TANNHELSE

2.1 Hvordan vurderer du din egen tannhelse?

	1	2	3	4	5	
Svært dårlig	☐	☐	☐	☐	☐	Svært god

2.2 Hvor fornøyd eller misfornøyd er du med tennene eller protesene dine?

	1	2	3	4	5	
Svært misfornøyd	☐	☐	☐	☐	☐	Svært fornøyd

BRUK AV HELSETJENESTER

3.1 Har du, grunnet egen helse, i løpet av de siste 12 måneder vært hos:

	Nei	Ja	Antall ganger
Fastlege/allmennlege	☐	☐	☐☐
Legevakt	☐	☐	☐☐
Psykiater/psykolog	☐	☐	☐☐
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	☐☐
Tannlege/tannpleier	☐	☐	☐☐
Apotek *(for kjøp/råd om medisiner/behandling)*	☐	☐	☐☐
Fysioterapeut	☐	☐	☐☐
Kiropraktor	☐	☐	☐☐
Akupunktør	☐	☐	☐☐
Alternativ behandler *(homøopat, soneterapeut, healer etc)*	☐	☐	☐☐
Tradisjonell helbreder *(hjelper, «læser» etc)*	☐	☐	☐☐
Har du kommunisert via internett med noen av tjenestene over?	☐	☐	☐☐

3.2 Har du i løpet av de siste 12 måneder vært på sykehus?

	Nei	Ja	Antall ganger
Innlagt på sykehus	☐	☐	☐☐
Konsultasjon ved sykehus uten innleggelse:			
Ved psykiatrisk poliklinikk	☐	☐	☐☐
Ved annen sykehuspoliklinikk	☐	☐	☐☐

BRUK AV MEDISINER

4.1 Bruker du, eller har du brukt, noen av følgende medisiner? *Sett ett kryss per linje.*

	Aldri	Nå	Før, ikke nå	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Annen medisin mot hjertesykdom *(f.eks. blodfortynnende, rytmestabiliserende, nitroglycerin)*	☐	☐	☐	
Insulin	☐	☐	☐	
Tabletter mot diabetes	☐	☐	☐	
Stoffskiftemedisin *(Levaxin/thyroxin)*	☐	☐	☐	

4.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner? *Sett ett kryss per linje.*

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende uten resept	☐	☐	☐	☐
Magesyrehemmende medisiner	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

4.3 Skriv alle medisiner (reseptfrie og reseptbelagte) du har brukt regelmessig siste 4 uker. *Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc.*

Får du ikke plass til alle medisinene, bruk eget ark.

KOSTHOLD

5.1 Spiser du vanligvis frokost hver dag?

☐ Nei ☐ Ja

5.2 Hvor mange porsjoner frukt og grønnsaker spiser du i gjennomsnitt per dag? *Med porsjon menes f.eks. et eple, en salatbolle.*

Antall porsjoner

5.3 Hvor ofte spiser du vanligvis disse matvarene? *Sett ett kryss per linje.*

	0–1 pr. mnd.	2–3 pr. mnd.	1–3 pr. uke	4–6 pr. uke	1 eller mer pr. dag
Rødt kjøtt *(alle produkter av storfe, får, svin)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei)*	☐	☐	☐	☐	☐
Feit fisk *(laks, ørret, uer makrell, sild, kveite)*	☐	☐	☐	☐	☐

5.4 Hvor mange glass/beger drikker/spiser du vanligvis av følgende? *Sett ett kryss per linje.*

	Sjelden/ aldri	1–6 pr. uke	1 pr. dag	2–3 pr. dag	4 eller mer pr. dag
Melk/yoghurt tilsatt probiotika *(Biola, Cultura, Activia, Actimel, BioQ)*	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker:					
med sukker	☐	☐	☐	☐	☐
med kunstig søtning	☐	☐	☐	☐	☐

5.5 Hvor mange kopper kaffe og te drikker du daglig? *Sett 0 for de typene du ikke drikker daglig.*

	Antall kopper
Filterkaffe *(trakterkaffe)*	
Kokekaffe og/eller presskannekaffe	
Pulverkaffe	
Espressobasert kaffe *(fra kaffemaskin, kapsler etc)*	
Sort te *(f.eks. Earl Grey)*	
Grønn/hvit/oolong te	
Urtete *(f.eks. nype, kamille, Rooibos)*	

HELSEBEKYMRING

	Ikke i det hele tatt	Litt	Noe	En hel del	Svært mye
6.1 **Tror du at det er noe alvorlig galt med kroppen din?**	☐	☐	☐	☐	☐
6.2 **Er du svært bekymret over helsen din?**	☐	☐	☐	☐	☐
6.3 **Er det vanskelig for deg å tro på legen din dersom hun/han forteller deg at det ikke er noe å bekymre seg for?**	☐	☐	☐	☐	☐
6.4 **Er du ofte bekymret for muligheten for at du har en alvorlig sykdom?**	☐	☐	☐	☐	☐
6.5 **Hvis du blir gjort oppmerksom på en sykdom (f.eks. via TV, radio, internett, avis eller noen du kjenner), bekymrer du deg da for selv å få sykdommen?**	☐	☐	☐	☐	☐
6.6 **Opplever du at du plages av mange ulike symptomer?**	☐	☐	☐	☐	☐
6.7 **Har du tilbakevendende tanker (som er vanskelig å bli kvitt) om at du har en sykdom?**	☐	☐	☐	☐	☐

FYSISK AKTIVITET

7.1 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?** *Sett kryss i den ruta som passer best.*

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks. pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

7.2 **Angi bevegelse og kroppslig anstrengelse i din fritid det siste året.** *Hvis aktiviteten varierer gjennom året, ta et gjennomsnitt. Sett kryss i den ruta som passer best.*

- ☐ Leser, ser på TV / skjerm eller annen stillesittende aktivitet
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka *(inkludert gang eller sykling til arbeidsstedet, søndagsturer etc)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking etc minst 4 timer i uka
- ☐ Trener hardt eller driver konkurranseidrett regelmessig flere ganger i uka

7.3 **Siste uka, omtrent hvor lang tid tilbrakte du <u>sittende</u> på en typisk hverdag og fridag?** *F.eks. ved arbeidsbord, hos venner, mens du så på TV / skjerm.*

☐☐ timer sittende på en hverdag *(både jobb og fritid)*

☐☐ timer sittende på en fridag

ALKOHOL

8.1 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2–4 ganger hver måned
- ☐ 2–3 ganger per uke
- ☐ 4 eller flere ganger per uke

8.2 **Hvor mange enheter alkohol (flaske øl, glass vin eller drink) tar du vanligvis når du drikker?**

1–2	3–4	5–6	7–9	10 eller flere
☐	☐	☐	☐	☐

8.3 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ Aldri
- ☐ Sjeldnere enn månedlig
- ☐ Månedlig
- ☐ Ukentlig
- ☐ Daglig eller nesten daglig

RØYK OG SNUS

9.1 **Har du røykt/røyker du daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

9.2 **Har du brukt/bruker du snus eller skrå daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

SPØRSMÅL OM KREFT

10.1 **Har du noen gang fått**

	Nei	Ja	**Hvis ja:** alder første gang	**Hvis ja:** alder siste gang
Utført mammografi	☐	☐		
Målt PSA (prostataspesifikt antigen)	☐	☐		
Utført tykktarmsundersøkelse (koloskopi, avføringsprøve)	☐	☐		

10.2 **Har noen i din nære biologiske familie hatt**

	Egne barn	Mor	Far	Mormor	Morfar	Farmor	Farfar	Tante	Onkel	Søsken
Brystkreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostatakreft	☐		☐		☐		☐		☐	☐
Tykktarmskreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

11.1 **Hva er din høyeste fullførte utdanning?** *Sett ett kryss.*

- ☐ Grunnskole/framhaldsskole/folkehøyskole inntil 10 år
- ☐ Fagutdanning/realskole/videregående/gymnas minimum 3 år
- ☐ Høyskole/universitet mindre enn 4 år
- ☐ Høyskole/universitet 4 år eller mer

11.2 **Hva var din husstands samlede bruttoinntekt siste år?** *Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.*

- ☐ Under 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ Over 1 000 000 kr

FAMILIE OG VENNER

12.1 **Hvem bor du sammen med?**

	Nei	Ja	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

12.2 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

12.3 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

12.4 **Hvor ofte deltar du vanligvis i foreningsvirksomhet som syklubb, idrettslag, politiske, religiøse eller andre foreninger?**

Aldri, eller noen få ganger i året	1–2 ganger i måneden	Omtrent 1 gang i uka	Mer enn 1 gang i uka
☐	☐	☐	☐

SPØRSMÅL TIL KVINNER

13.1 **Hvor gammel var du da du fikk menstruasjon første gang?**

Alder

13.2 **Er du gravid nå?**

☐ Nei ☐ Ja ☐ Usikker

13.3 **Hvor mange barn har du født?**

Antall barn

13.4 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.** *Angi så godt du kan. Hvis flere barn, bruk ekstra ark.*

	Fødselsår	Fødselsvekt i gram	Ammet ant. mnd.
Barn 1			
Barn 2			
Barn 3			
Barn 4			
Barn 5			
Barn 6			

SPØRSMÅL TIL MENN

14.1 **Har du fått behandling for betennelse i prostata eller urinblæra?**

☐ Nei ☐ Ja

14.2 **Har du fått utført steriliseringsoperasjon?**

☐ Nei ☐ Ja **Hvis ja:** hvilket år

Tusen takk for ditt bidrag.

Appendix E

Approval from the Regional Committee for Medical and Health Research Ethics

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			10.10.2017	2017/1973/REK nord
			Deres dato:	Deres referanse:
			19.09.2017	

Vår referanse må oppgis ved alle henvendelser

Bente Morseth
Institutt for idrettsfag/Institutt for samfunnsmedisin

2017/1973 Fysisk aktivitet, aldring og hjertet

Forskningsansvarlig institusjon: UiT - Norges arktiske universitet
Prosjektleder: Bente Morseth

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden er behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) ved sekretariatsleder, på fullmakt gitt av komiteen med hjemmel i forskningsetikkforskriften § 10 annet ledd. Søknaden er vurdert med hjemmel i helseforskningsloven.

Prosjektleders prosjektomtale
Aldring er assosiert med en svekkelse av hjertes struktur og funksjon, samt økt risiko for arytmier som atrieflimmer. Fysisk aktivitet har en positiv effekt på risiko for hjerte- og karsykdom, men mekanismene bak denne effekten er lite kjent. Prosjektet har som mål å gi ny kunnskap om effektene av fysisk aktivitet på hjertets struktur og funksjon, og særlig betydningen av fysisk aktivitet for den aldersrelaterte svekkelsen av hjertets funksjon. Datamaterialet hentes fra Tromsøundersøkelsens 7. runde (Tromsø 7) som ble gjennomført i 2015-2016. Fysisk aktivitet ble målt ved bruk av objektive målemetoder (akselerometer, ActiGraph og Actiwave Cardio) på 6300 deltakere, og hjertestruktur og -funksjon ble målt ved bruk ekkokardiografi (2384 deltakere) og EKG (12-lead, 7784 deltakere), samt 1-lead EKG i 24 timer ved bruk av Actiwave Cardio (700 deltakere). I tillegg ble det samlet en rekke data på helse og livsstil fra spørreskjema, kliniske undersøkelse og blodprøver.

Vurdering

Prosjektet vil benytte demografiske data, antropometriske data, aktivtetsdata, blodprøver og kliniske data fra alle som har som har gyldige målinger av fysisk aktivitet (6300), EKG (7784) og ekkokardiografi (2384) i Tromsø 7.

Vurdering av om det avgitte samtykket er dekkende
Prosjektet vil kun benytte seg av allerede innsamlet materiale som ligger innenfor hovedformålet med Tromsøundersøkelsen. Skriftlig samtykke er innhentet, og deltakerne kan til enhver tid reservere seg mot at deres data blir brukt i analyser.

Etter fullmakt er det fattet slikt

vedtak
Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 31.01.2022, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Kopi til:postmottak@uit.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Monika Rydland	77620756	16.03.2021	20828
			Deres referanse:	

Bente Morseth

20828 Fysisk aktivitet, aldring og hjertet

Forskningsansvarlig: UiT Norges arktiske universitet

Søker: Bente Morseth

REKs vurdering

Vi viser til søknad om prosjektendring for ovennevnte forskningsprosjekt mottatt 09.03.2021. Søknaden er behandlet av sekretariatet i REK nord på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Av endringssøknaden fremgår det at prosjektperioden søkes forlenget til 31.12.2023 og at man ønsker å benytte data fra Tromsø 4-6, ikke bare Tromsø 7 som tidligere godkjent.

Videre planlegger man bruk av data fra Birkebeinerstudien. Prosjektleder skriver: *"Vi har planlagt bruk av data fra Birkebeinerstudien i artikkel 3. Birkebeinerstudien er omtalt i REK-prosjekt 175586 Fysisk aktivitet, atrieflimmer og forebygging av slag og død, og de samme dataene vil bli benyttet i dette prosjektet. Det vil (som beskrevet i sak 175586) bli innhentet nytt samtykke fra deltakerne i Birkebeinerstudien vedrørende kobling til nasjonale helseregistre og befolkningsundersøkelser (Tromsøundersøkelsen og HUNT). Det nye samtykkebrevet er vedlagt denne henvendelsen og er identisk med samtykkebrevet i sak 175586."*

REK har ingen innvendinger til forlengelse av prosjektperiode og heller ikke til å inkludere data fra Tromsø 4-6.

Når det gjelder inkludering av data fra Birkebeinerstudien så ser vi at det i samtykkeskriv vedlagt endringssøknaden bes om samtykke til å bruke data i prosjektet "The Norwegian Exercise in Atrial Fibrillation Multicentre Study" (NEXAF). Fysisk aktivitet, aldring og hjertet er ikke nevnt i skrivet. REK finner det derfor ikke dekkende for bruk i dette prosjektet.

Informasjonsskrivet må endres slik at det fremgår at data skal brukes i begge prosjektene og det må godkjennes for bruk i begge prosjektene.

Etter fullmakt er det fattet slikt

Vedtak

Godkjent

Med hjemmel i helseforskningsloven § 11 godkjennes prosjektendringene.

Prosjektet er godkjent frem til ny omsøkt sluttdato 31.12.2023.

Av dokumentasjonshensyn skal opplysningene oppbevares i fem år etter prosjektslutt. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll. Prosjektdata vil således ikke være tilgjengelig for prosjektet. Prosjektleder og forskningsansvarlig institusjon er ansvarlige for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil.

Etter denne femårsperioden skal opplysningene slettes eller anonymiseres. Komiteen gjør oppmerksom på at anonymisering er mer omfattende enn å kun slette koblingsnøkkelen, jf. Datatilsynets veileder om anonymiseringsteknikker.

Vi gjør samtidig oppmerksom på at etter personopplysningsloven må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Før endringen igangsettes må informasjonsskriv revidert i tråd med ovennevnte sendes inn og godkjennes. Skrivet sendes via prosjektmappen i REK-portalen.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Søknad om å foreta vesentlige endringer
Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

Sluttmelding
Søker skal sende sluttmelding til REK nord på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.