UiT The Arctic University of Norway

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Clinical characteristics, echocardiographic indices of heart failure and mortality in a general population

The Tromsø Study

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Summary

Background Heart failure (HF) is a syndrome associated with high mortality rates, reduced quality of life and increased burden on the healthcare system. Ageing of the general population, declining incidence of myocardial infarction (MI) and improvements in medical treatment have resulted in an increase in HF prevalence especially HF with preserved ejection fraction (HFpEF) or diastolic HF. At the same time, number of studies on echocardiographic indices of diastolic dysfunction, left ventricle (LV) deformation parameters and its link to all-cause mortality and HF are scarce, as are studies describing clinical characteristics distinguishing between HF and chronic obstructive pulmonary disease (COPD), the two main causes of dyspnea in a general population.

Objective To study long-term risk of all-cause mortality using diastolic dysfunction indices in a population-based cohort. To describe peak-myocardial global longitudinal strain (GLS) in Norwegian general population sample, its relation to cardiovascular disease (CVD) risk factors and subclinical stage A HF (SAHF). To determine how abnormal lung sounds and respiratory symptoms may predict HF and COPD and estimate the overlapping grade of these diseases in a general population.

Methods Individuals with performed echocardiography and measured indices of diastolic dysfunction from the Tromsø 4-6 surveys were included in the analyses of all-cause mortality. Myocardial GLS, HF and COPD analyses were performed on persons who underwent echocardiographic assessment in the Tromsø 7 Study. Subjects were followed-up over 23 years and risk of death was calculated for left atrial (LA) diameter, mitral peak E deceleration time (DT), mitral peak E to peak A (E/A) ratio and mitral peak E to tissue Doppler peak e´ (E/e´) ratio values. GLS values were assessed in healthy individuals, persons with/without SAHF and those with various levels of systolic blood pressure (SBP). Values of abnormal GLS were analysed with respect to CVD risk factors. HF and COPD co-existence was estimated by echocardiography and spirometry using the latest guideline-based recommendations. Statistical methods included fractional polynomials, receiver operating characteristic (ROC), time-dependent Cox, linear and logistic regression and reliability analyses.

Main results Echocardiographic markers of diastolic dysfunction showed U-shaped associations with all-cause mortality outcome except of E/e´ which showed cubic association with an outcome. Combination of DT with LA diameter was preferable while assessing risk of all-cause mortality. Mean myocardial GLS (SD) in healthy individuals was -15.9 (2.7)% in men and -17.8 (3.1)% in women. In general population sample GLS declined with the age in healthy individuals of both sexes. Majority of studied CVD risk factors were associated with abnormal GLS. SBP increase was associated with myocardial GLS decline in women. Mean myocardial GLS values in individuals with SAHF were lower than in those without SAHF (-16.7% vs -17.9%, respectively; $p < 0.001$). Age-standardized

prevalence rates of HF and COPD in general population sample were 6.1% and 6.8%; 5.1% and 5.2% for men and women, respectively. Co-existent pathology was found in 9.2% of those with established COPD and HF diagnoses. Main predictors of COPD were wheezes while basal bilateral inspiratory crackles were more common for HF.

Conclusions Small atrial diameter is associated with increased all-cause mortality risk. Predictive ability of the outcome-derived cutoff points of LA diameter, DT and E/A ratio is similar to normalcy derived cutoff points used in recent guidelines. E/A ratio do not add incremental value while assessing all-cause death risk. Mean myocardial GLS declined with age in both sexes in general and in healthy participants. GLS was decreased in subjects with SAHF. The differential diagnosis between HF and COPD in the clinical settings can be based on history, symptoms and signs. Shortness of breath and abnormal lung sounds may be found in both diseases. Wheezes are an independent predictor of COPD and elevated proBNP of HF.

Abbreviations

2D – two dimentional
ACCF – American College of Cardiology Foundation
ACE – Angiotensin converting enzyme
AFI – automated function imaging
AHA- American Heart Association
AHT – antihypertensive treatment
ASE – American Society of Echocardiography
AUC – area under the curve
BMI – body mass index
BNP – Brain natriuretic peptide
BSA – body surface area
CAD – coronary artery disease
CI – confidence interval
COPD – chronic obstructive pulmonary disease
CR – coefficient of repeatability
CVD – cardiovascular disease
DBP – diastolic blood pressure
DT – mitral peak E deceleration time
E/A – mitral peak E to mitral peak A ratio
E/e´ - mitral peak E to tissue Doppler peak e´ratio
EACVI – European Association of Cardiovascular Imaging
ECG – electrocardiography
EDPVR – end-diastolic pressure-volume relationship
EDV – end-diastolic volume
EF – ejection fraction
ESC – European Society of Cardiology
ESPVR – end-diastolic pressure-volume relationship
ESV – end-systolic volume
FEV_1 – forced expiratory volume in 1 second
GLS – global longitudinal strain
HbA1c – glycated haemoglobin
HF – heart failure
HFmrEF – heart failure with mid-range ejection fraction
HFpEF – heart failure with preserved ejection fraction
HFrEF – heart failure with reduced ejection fraction
HR – hazard ratio
ICC – intraclass-correlation coefficient
IVS – interventricular septum
LA – left atrium
LAE – left atrial enlargement
LAVi – left atrial volume index
LLN – lower limit of normal
LV – left ventricle
LVEF – left ventricle ejection fraction
LVH – left ventricle hypertrophy
LVID – left ventricle internal diameter
LVMM – left ventricle myocardial mass
LVMMi – left ventricle myocardial mass index
MI – myocardial infarction
mMRC – modified medical research council (scale)
Nt-proBNP – N-terminal pro b-type natriuretic peptide
NYHA – New-York Heart Association
OR – odds ratio
PA – physical activity
PIN – personal identification number
PWT – posterior wall thickness
ROC – receiver operating characteristic
ROI – region of interest
RWT – relative wall thickness
SAHF – subclinical (class A) heart failure
SBP – systolic blood pressure
SD – standard deviation
SpO_2 – oxygen saturation
SV – stroke volume
TDI – Tissue Doppler imaging

List of papers

Paper I

Stylidis M, Sharashova E, Wilsgaard T, et al. **Left atrial diameter, left ventricle filling indices, and association with all-cause mortality: Results from the population-based Tromsø Study.** Echocardiography. 2019; 00:1-12. https://doi.org/10.1111/echo.14270

Paper II

Stylidis, M., Leon, D.A., Rösner, A. *et al.* **Global myocardial longitudinal strain in a general population—associations with blood pressure and subclinical heart failure: The Tromsø Study.** *Int J Cardiovasc Imaging* 36**,** 459–470 (2020). https://doi.org/10.1007/s10554-019-01741-3

Paper III

Melbye, H., Stylidis, M., Aviles-Solis, J.C. et al. **Prediction of chronic heart failure and COPD in a general population. The Tromsø Study.**

Submitted in ESC Heart Failure

1 Introduction

1.1 Heart Failure

1.1.1 Heart failure definition and classification

Heart failure (HF) defined as a clinical syndrome characterized by typical symptoms (breathlessness, ankle swelling, fatigue) that may be accompanied by signs (elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (1).

Current HF classification is based on left ventricle ejection fraction (LVEF) measurements. The LVEF threshold of >50% reflects normal ejection fraction (EF). Grading of the different types of HF is summarized in Table 1 (1).

Table 1. Definition of the heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) (1)

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	-	1. Elevated level of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction	1. Elevated level of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction

BNP: B-type natriuretic peptide; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LAE: left atrial enlargement; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; Nt-proBNP: N-terminal pro-B type natriuretic peptide.

[a]Signs may not be resent in the early stages of HF (especially in HFpEF) and inpatients treated with diuretics.

[b]BNP >35 pg/mL and/or Nt-proBNP >125 pg/mL

1.1.2 Heart failure aetiology

Aetiology of HF is complex and diverse. Latest reports consider HF phenotyping as proper way for distinguishing HF subtypes and treatment strategies. Thus, Berlot et al. divides HF phenotypes by two large groups: hypertrophied phenotypes and dilated phenotypes (2). Main aetiologies of hypertrophied phenotypes are the hypertensive heart disease resulting in concentric remodelling, concentric hypertrophy and infiltrative myocardial disease (amyloidosis). Dilated phenotypes are mainly caused by response to loading conditions abnormalities, for example in cardiomyopathies including idiopathic, valvular heart disease, congenital diseases (2). Other authors suggest more comprehensive division of hypertrophied phenotype by several groups referring to clinical presentation and predisposition phenotypes (3). Clinical presentation of heart failure with preserved ejection fraction (HFpEF) phenotypes are lung congestion, chronotropic incompetence, pulmonary hypertension, skeletal muscle weakness, atrial fibrillation. Predisposition phenotypes include overweight/obesity/metabolic syndrome/diabetes, arterial hypertension, renal dysfunction and coronary artery disease (CAD) (3).

HF aetiology depends on world regions and the prevalence of cardiovascular and non-cardiovascular risk factors. However, the three main aetiological groups should be mentioned. These include conditions related to diseases of the myocardium (ischemic heart disease, toxic damage, infiltration, genetic abnormalities), abnormal loading conditions (hypertension, valve and myocardium structural defects, high output states, volume overload) and arrhythmias (tachy- and bradyarrythmias) (1). The most common aetiologies of HF in Europe are the arterial hypertension and ischemic heart disease (4).

1.1.3 Heart failure pathophysiology

Pathophysiology of chronic HF includes period of latent or asymptomatic left ventricular (LV) dysfunction prior of the signs and symptoms development (5). Literature data showed that asymptomatic LV dysfunction was found in 1.5% of healthy individuals aged 25-74 years during echocardiographic investigations (6). The preceding “index event” such as myocardial infarction (MI) with loss of contractile tissue, myocarditis, systemic hypertension, pressure overload or genetic abnormalities can lead to the progression of HF. The underlying process of an index event is often poorly understood or unknown, for example in persons with idiopathic dilated cardiomyopathy. Further structural remodelling of the heart and disease progression includes myocyte hypertrophy, increased wall stress, fibrosis, cell necrosis and apoptosis, neuroendocrine activation and cytokine release. Final stages of congestive HF are associated with salt and water retention, oedema and low cardiac output (7). HF pathophysiology paradigms have been changing over time from “Hemodynamic model” in 1950s-1980s to “Neurohormonal model” in 1980s-2000 mostly due to growing evidence of the angiotensin converting enzyme (ACE) inhibitors and adrenergic β-blockers beneficial effect on survival of HF patients (8-10).

1.1.4 Sex differences in heart failure

Despite of similar symptoms of HF in both men and women they differ primarily by more severe dyspnea, oedema, and fatigue in women along with a worse quality of life (11). Elderly women with hypertension are more likely than men to have HFpEF (12). Due to physiological sex differences, hemodynamic stress related myocardium remodelling is primarily concentric hypertrophy in women while in men eccentric remodelling pattern is predominant (13, 14). Some of the cardiovascular disease (CVD) risk factors especially diabetes and obesity are found to increase the risk of heart failure with reduced ejection fraction (HFrEF) more in women than in men (15, 16). However women with HFrEF have better survival profile compared with men (17).

1.1.5 Heart failure prognosis

In cohort studies on prognosis of individuals with chronic HF, a 1-year survival rate of 80-90% was reported for outpatient HF patients compared to 97% in the general population without HF (18). The 5-year survival rate were 50-60% for outpatient HF patients and 85% in the general population. In UK 10-year survival in a community-based study was 27.4% with 75% in general population (18). Recent European Society of Cardiology (ESC) HF guidelines refer to meta-analyses results reported by Rahimi K. et al. and Ouwerkerk W. et al. in year 2014 (19, 20). In the study by Outwerkerk W., et al. 117 prediction models in 55 papers were identified. The number of variables used was 249. C-statistics of 0.71±0.001, 0.68±0.001 and 0.63±0.001 for models predicting mortality, HF hospitalization, or both, were reported. Rahimi K. et al., showed that death prediction models had better discriminative ability compared to death and hospitalization models and hospitalisation models alone (p=0.0003). Among the strongest death predictors were: age, renal function, blood pressure, blood sodium level, LVEF, sex, N-terminal pro b-type Natriuretic Peptide (Nt-proBNP) level, New-York Heart Association (NYHA) functional class, diabetes, body mass index (BMI). In overall, models described in these two studies showed only a moderate accuracy of predicting mortality and other endpoints such as death and hospitalisation or hospitalisation only (1).

1.2 Epidemiology of Heart Failure

In the adult population of developed countries, HF prevalence is 1-2%. Prevalence of HF increases progressively with the age and among individuals >70 years prevalence reaches up to 10% (1). The prevalence varies in different populations. Thus, in US (Olmsted County, Minnesota; 1997-2000) HF prevalence was 2.2% (95%CI 1.6-2.8%) with an increase up to 8.4% for those aged ≥75 years (21). Results of the Rotterdam study (1998) showed 0.9% of HF prevalence in 55-64 years age group, 4% in those with 65-74 years age, 7% in age group 75-84 years and >10% in those aged ≥85 years (22). The HF prevalence approved by Doppler echocardiography in MONICA Study (1995) was 15.8% for individuals aged >65 years (21). In UK age and sex-standardized prevalence of HF remains stable in

the range of 1.5-1.6% (2002-2014) however with an increase in absolute number of people affected with HF by 23% over the same time period (23).

The lifetime risk of HF is 33% for men and 28% for women at the age of 55 years (22). The mean age (standard deviation) (SD) of those getting a HF diagnosis was 76.7 (12.6) years (24). The incidence of HF varies from 5 to 10 per 1000 persons per year (21). Data from Hillingdon HF study showed an incidence about 0.2/1000 person-years in age group of 45-55 years to 12.4/1000 person-years in those aged >85 years (25). According to the Rotterdam study the incidence of HF was 2.5/1000 person-years in age of 55-64 years and 44/1000 person-year in age >85 years (22).
HF is more frequent in men than in women (15 and 12 per 1000 persons per year) (22). HF incidence trends over time showed a decline in women by 30-40% according the Framingham Heart Study, however in men incidence did not changed over 50 years (1950-1999) (26). The Olmsted County (Minnesota) population-based study results also showed no change in HF incidence from 1979 until 2000 (27). Data from the latest large population-based study conducted in UK on 4 million individuals showed HF incidence standardized by age and sex had declined by 7% both in men and women from 2002 until 2014 (338 to 332 per 100000 person-years). In the same period the absolute number of newly diagnosed HF in UK increased by 12% (23).
A number of studies show a modest decrease of HF incidence over the last decades associated with decreasing incidence of MI and higher survival of post-MI patients due to improved medical treatment (25, 28, 29).

The number of comorbidities (SD) in patients with incident HF increased over time from 3.4 (1.9) in 2002 to 5.4 (2.5) in 2014. The five most common comorbidities were hypertension (67%), ischemic heart disease (49%), osteoarthritis (43%), atrial fibrillation (40%), and dyslipidaemia (28%) (23).

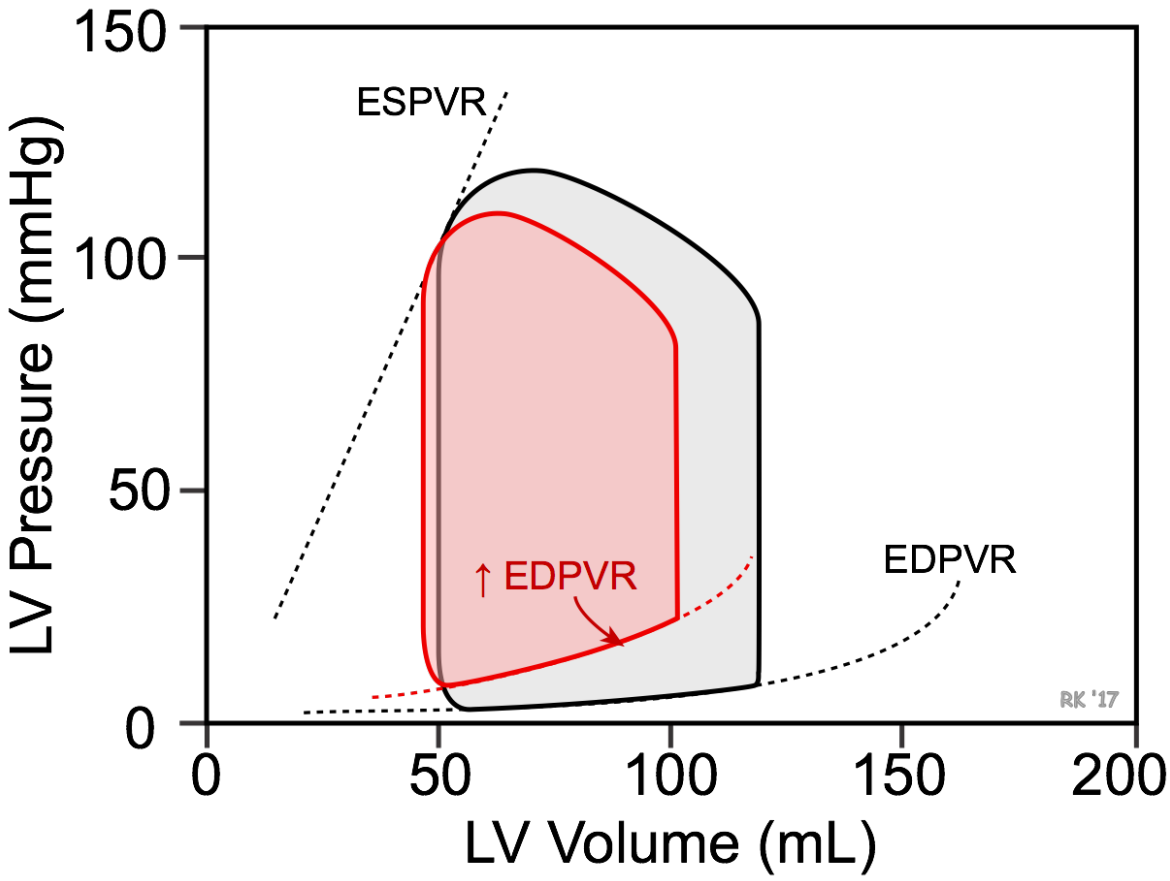
According to the latest data from The Norwegian Institute of Public Health the age and sex-adjusted HF incidence had a small decline in the period of 2012 to 2018 from 349 to 340 per 100000 person-years (30). Norway is in line with other high-income countries with similar patterns in HF incidence decline over time. Thus, incidence declined by 12.2% in men and by 17.2% in women from 2000 to 2014. HF incidence remained unchanged in those aged 50 years or younger (31).

1.3 Diastolic heart failure in the general population. Role of Doppler indices

Diastolic HF is characterized as a progressive disorder associated with impaired LV relaxation, increased LV stiffness, increased interstitial collagen deposition, and modified extracellular matrix proteins (32). HF caused by diastolic dysfunction is usually referred to as HFpEF. Assessment of the

diastolic function includes measurement of pressure-volume relationship. The change in the pressure-volume relationship in presence of diastolic dysfunction is shown in Figure 1.

Figure 1. Pressure-volume loops in normal heart and in diastolic dysfunction. Image owned by Richard Klabunde, used with permission



ESPVR: end-systolic pressure-volume relationship; EDPVR: end-diastolic pressure-volume relationship.

In diastolic dysfunction (red loop) the ventricular compliance is reduced along with impaired ventricular relaxation. End-diastolic pressure-volume relationship (EDPVR) slope increases resulting in less ventricular filling and increased LV filling pressure. This leads to a decrease of stroke volume (SV) indicated by the width of the pressure-volume loop and cardiac output simultaneously with the presence of normal or slightly reduced LVEF.

In most of the community-based studies around half of the patients diagnosed with HF had HFpEF (33). The prevalence of HFpEF in population increases with age and it is higher in any given age in women than in men. Female patients are more likely to develop HFpEF partly due to women's longer life expectancy causing a higher proportion in the general population above 75 years to be women

(approximately 60% of the population) (17). However, despite of more women being at risk of HFpEF, adjustment for HFpEF risk factors such as age, obesity, blood pressure and its treatment, and especially previous MI, reduces risk of HFpEF in women compared to men (34).
Age and sex-adjusted HFpEF incidence from 2000 to 2010 declined by 28% according the data from Olmsted County (Minnesota) study (35). Age, female sex and ethnicity (white rather than black or Hispanic women) remain the most important non-CVD risk factors for development of HFpEF. CVD risk factors such as hypertension, diabetes, obesity, atrial fibrillation are more prevalent in patients with HFpEF rather than HFrEF (17).
Kuznetsova et al. reported the overall prevalence of LV diastolic dysfunction in a random general population sample estimated from echocardiographic measurements as 27.3% according to the broader definition before 2016 ESC guidelines (32). Due to increasing life expectancy, growing diastolic HF prevalence is placing an increasing burden on healthcare (23).

The measuring of pressure-volume relationship is considered as the gold standard for assessing diastolic HF, however it requires an invasive approach (32). With the evolving of ultrasound, Doppler derived indices opened the opportunity of non-invasive evaluation of the diastolic function (36). Among these indices is the ratio of the maximal early diastolic E wave velocity to peak velocity flow in late diastole – A-wave. Another index widely used for evaluation of diastolic dysfunction is the deceleration time of the early diastolic flow E wave (DT). Both indices provide prognostic information and used for grading the diastolic dysfunction and evaluating the LV filling pressures (37-39). Ratio between early diastolic peak E-wave velocity and tissue Doppler (TDI) derived mitral annular early diastolic velocity peak e` (E/e` ratio) also treated as important parameter associated to LV filling pressures, diastolic dysfunction and prognosis (40). Finally, an enlarged left atrial (LA) size appears to be an independent risk factor of adverse cardiovascular events (41) and marker of diastolic HF.

1.4 Heart Failure and Chronic Obstructive Pulmonary Disease. Prevalence and difficulties in diagnostics

Chronic obstructive pulmonary disease (COPD) appears as one of the most common comorbidity in HF. One third of the individuals with HF are presenting with COPD symptoms (42, 43). However, COPD diagnostics in co-existence with HF is difficult. According to recent reports, the prevalence of HF in COPD patients is underdiagnosed due to interference of COPD with the HF's diagnostic process (42). Lack of routine use of spirometry in patients with HF is considered as one of the main reasons for underestimation of co-existent COPD (44). Therefore, majority of registry-based information on COPD in HF patients is still based on questionnaire data rather than on spirometry findings (44). Similarly, HF is underdiagnosed in COPD patients with a following underuse of β-blockers and increased mortality and number of hospitalisations (44). The growing body of evidence from

observational studies on COPD patients suggests that β-blockers use is associated with prolonged survival and lower number of COPD exacerbations (45). On the other hand there is no evidence up to date on improvement of long-term survival by treatment of COPD (45).

Another important challenge of co-existent HF and COPD pathology research is assessment of the associations between COPD and different subtypes of HF (HFrEF, heart failure with mid-range ejection fraction (HFmrEF) and HFpEF) in patients with dyspnea. According to latest report of Nielsen et al. which included patients hospitalized with dyspnea, 10% of patients with dyspnea had HFmrEF, and 41% had HFpEF. Of those with presumed non-cardiac dyspnea, 71% had HFpEF after examination with echocardiography and Nt-proBNP (46), more due to LV hypertrophy than diastolic dysfunction.

1.5 Speckle-tracking derived myocardial strain and its role in cardiovascular disease research

1.5.1 Myocardial strain. Basic concepts.

The word "Strain" can be interpreted as "stretching" or in scientific settings as "deformation". The common definition of strain is a deformation of the object, relative to its original length (47). Linear strain is defined by the following formula:

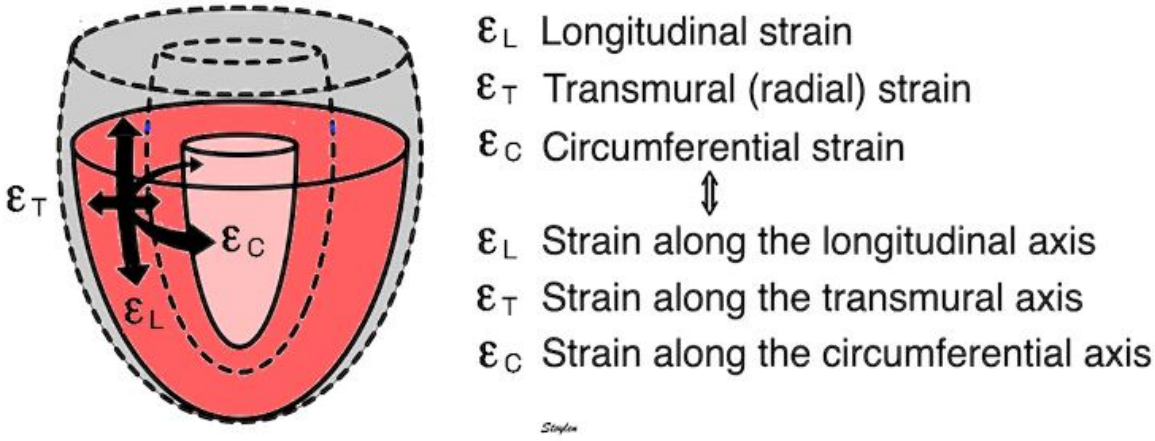
$$\varepsilon = \frac{L - L_0}{L_0} = \frac{\Delta L}{L_0}$$

where ε is strain; L_0 is baseline length and L is the instantaneous length of the object at the time of measurement. Strain values could be obtained with the use of Tissue Doppler imaging or with the speckle-tracking technology. In our study strain values were derived by speckle-tracking – the principle which based on definition of myocardial region (kernel) in one frame and further identification of this region in the next frame with same shape, size and speckle pattern (48).

Two approaches of strain are used nowadays. First one is the linear or Lagrangian strain which was described above. The second concept is Eulerian or "natural" strain. The main difference between two concepts is that reference length (L_0) in Lagrangian strain is defined against all occurred deformation (49). In Eulerian strain the reference length is changing in dependence to deformation of the object in certain time moment, reflecting instantaneous change of myocardial length. If the strain values are derived from speckle-tracking technique use of Lagrangian strain is recommended. Eulerian strain values used mainly in Doppler-derived strain. Strain is expresses in percent with or without negative sign depending on type of ongoing change of myocardial length. Thus, positive strain is associated with lengthening and stretching of myocardium therefore negative strain is associated with shortening

and compression (47). To avoid the possible confusion while comparing strain between individuals we used absolute values of strain as it was recommended by European Association of Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) Industry Task Force (49). Thus, the number is becoming more negative when global longitudinal strain (GLS) increases and becomes less negative when GLS decreases together with LV function impair. The deformation of the heart is three dimensional and therefore three measures of myocardial strain are usually described in literature. These are: longitudinal strain, transmural (radial) strain and circumferential strain (Figure 2).

Figure 2. Three dimensional model of LV deformation. Image owned by Asbjørn Støylen. Used with permission



In this thesis we focused our research on longitudinal motion of the heart (global longitudinal strain) in healthy individuals and in persons with different CVD's.

1.5.2 Global longitudinal strain role in cardiovascular diseases research

Increased CVD burden creates challenges on both healthcare and individual level. Therefore, medical society focused on producing and evolving of novel contemporary, robust, accessible and precise diagnostic methods which could play a major role in primary and secondary CVD prevention strategies. The evidence on associations of GLS with different CVD's has been growing in the last decades and routine assessment of the GLS in clinical settings appears beneficial. GLS was recognized as a better metric for cardiac dysfunction than EF (50). GLS is a good marker of subtle impairments of myocardial function in CVD and particularly in HF. Thus, Sucato et al. reported on GLS decline in those with HFpEF compared to the control population due to coronary microvascular dysfunction (51). GLS is able to predict HF decompensation in patients with LV systolic dysfunction (52), has incremental predictive value and independently associated with atrial fibrillation (53). Layer-specific

myocardial strain showed significant impairment in patients with CAD (54). GLS showed independent association with post-discharge HF in patients underwent reperfusion therapy (55). The nowadays issue is that the values of normal GLS on population level have not been defined. Current guidelines (56) report only the approximate threshold of GLS of -20% expected in healthy persons pointing on heterogeneity of GLS in published literature. Despite of number of meta-analyses (57, 58) and single studies on GLS normalcy (59, 60) the GLS threshold applicable for use in clinical settings is yet to be defined.

2 Aims of the thesis

I. To explore the associations between diastolic dysfunction indices and long-term risk of all-cause mortality in adults over a 23-years follow-up period.

II. To study peak-myocardial GLS in a large population sample from Norway and its relation to established CVD risk factors. To determine GLS normal thresholds in healthy individuals and the relation of myocardial GLS to stage A subclinical heart failure (SAHF).

III. To determine how abnormal lung sounds and respiratory symptoms may predict HF and COPD, and to what extent the occurrence of these diseases overlap in general population.

3 Materials and methods

3.1 The Tromsø Study

The Tromsø Study is the population-based longitudinal single-centre study conducted in the Tromsø municipality of Norway. The study was initiated in 1974 with the aim of assessing the causes of high cardiovascular mortality in male population of Northern Norway (61). Since the beginning, seven consecutive surveys were conducted and referred as: Tromsø 1 (1974), Tromsø 2 (1979-1980), Tromsø 3 (1986-1987), Tromsø 4 (1994-1995), Tromsø 5 (2001-2002), Tromsø 6 (2007-2008), and Tromsø 7 (2015-2016). The field of the surveys expanded to both genders in 1979 and gradually to a wide specter of chronic diseases.

Both total birth cohorts and random samples of the Tromsø municipality residents were invited to a first visit in the Tromsø 1-3 and the Tromsø 5-6 surveys. In the Tromsø 4 survey the invitation was sent to all citizens of Tromsø aged 25 years or older, and in the Tromsø 7 survey to all citizens of age 40 years and above. New birth cohorts were added during the Tromsø 1-4 surveys. The Tromsø 4-7 surveys included a second visit with an extensive examination. The attendance rates were higher than 75% in the Tromsø 1-5 surveys with a decline in the Tromsø 6 and 7 Tromsø surveys (66% and 65%, respectively) (62, 63).

The surveys had similar design. Invitation was sent to the potential participants by mail two weeks prior the time of appointment. The invitation leaflet included information about the survey and a first questionnaire. One reminder was given to non-attendees (61). The Tromsø 1 survey questionnaire included information on family history of CVD and symptoms, diabetes, physical activity, smoking, ethnicity and employment. In the later surveys, both the first and the second questionnaires were expanded with information on other diseases, dietary habits, use of medication, lifestyle characteristics, socio-economic status and use of the healthcare services. Participants were asked to return the second questionnaire by mail in a pre-addressed envelope. More than 90% of the survey participants returned the second questionnaire (61).

The Tromsø Study has been approved by the Regional Committee for Medical Research Ethics, North Norway and by the Data Inspectorate. The Study conformed to the principles outlined in the 1964 Declaration of Helsinki. Informed consent was obtained from all individual participants included in the Tromsø 4-7 surveys. The Tromsø Study web resource (www.tromsoundersokelsen.no) provides information on questionnaires, invitation letters, consent forms and study data. Direct weblinks to the forms listed above are available in the Appendix.

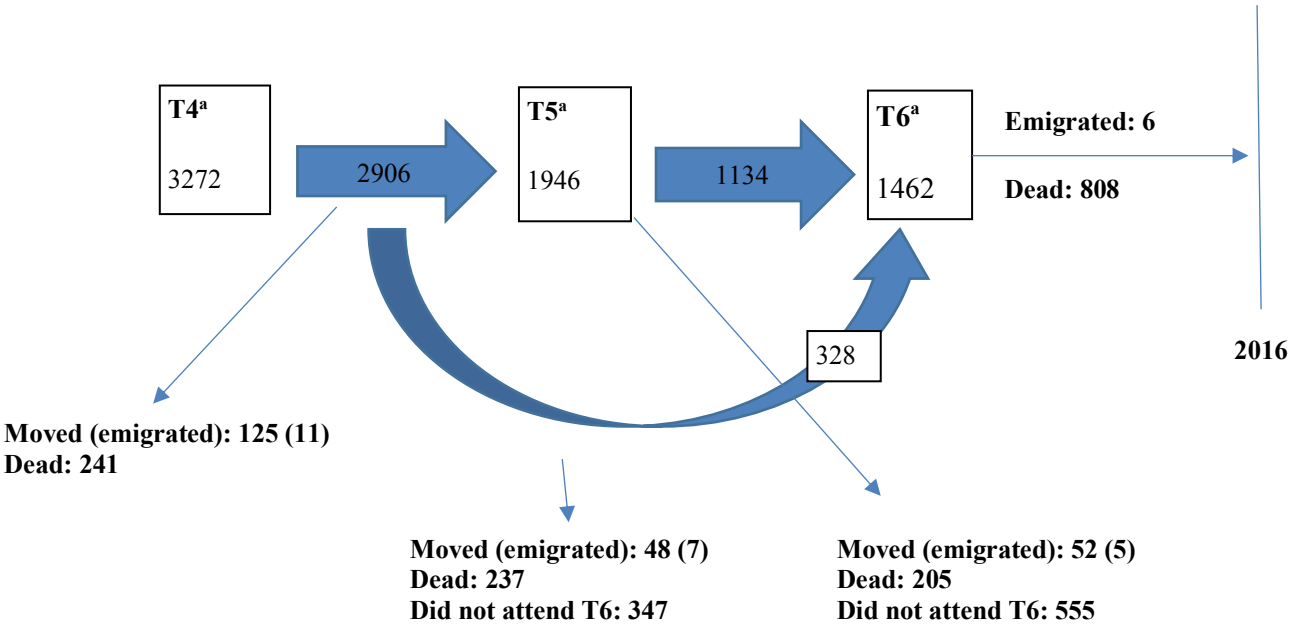
3.2 Study population

Paper I used the Tromsø 4 survey as the baseline survey and included a random selection of 3272 participants who underwent echocardiography (Figure 3). From this subsample 1946 and 1462 individuals participated in echocardiographic examination in the Tromsø 5 and/or Tromsø 6 surveys, respectively. We excluded individuals aged 50 years or younger (n=470), those with atrial fibrillation (n=39) and individuals with LVEF <50% (n=37) to prevent potential inaccuracy and misinterpretation of DT measurements leaving 2734 participants for analysis. Due to missing data on left atrial (LA) diameter, DT and mitral peak E to peak A (E/A) ratio the final participant numbers for these parameters were slightly smaller: 2616 individuals for LA diameter analysis, 2691 individuals for DT analysis and 2699 individuals for E/A ratio analysis. In addition, 1875 Tromsø 6 survey participants were included in E/e´ ratio analysis.

In Paper II we assessed GLS in the general population sample in the Tromsø 7 survey and explored its associations with blood pressure and SAHF. The subsample in Paper II included 840 men and 1015 women from the Tromsø 7 survey (total n=1855) aged 40-99 years with measured GLS. We excluded 108 individuals with missing data for any of the following variables: MI, angina, stroke, bronchitis, hypertension, diabetes, atrial fibrillation, HF, glycated haemoglobin (HbA1c), LVEF. Thus, data on 1747 individuals was used in analyses of myocardial GLS and its associations with blood pressure along with age- and sex-specific analysis of myocardial GLS in healthy individuals. Healthy persons were defined as those without known CVD´s and comorbidities (n=1068). We excluded those with hypertension, diabetes, atrial fibrillation, HF, angina, MI, stroke, COPD, LVEF <50% from healthy subsample. For the assessment of GLS in those with SAHF we excluded 1146 individuals with known CVD, LV geometric abnormalities and severe valvular heart disease from the total (n=1855) subsample, leaving 709 subjects who may include SAHF. After applying the SAHF criteria on selected population, we identified 220 of 709 individuals with SAHF (Figure 4).

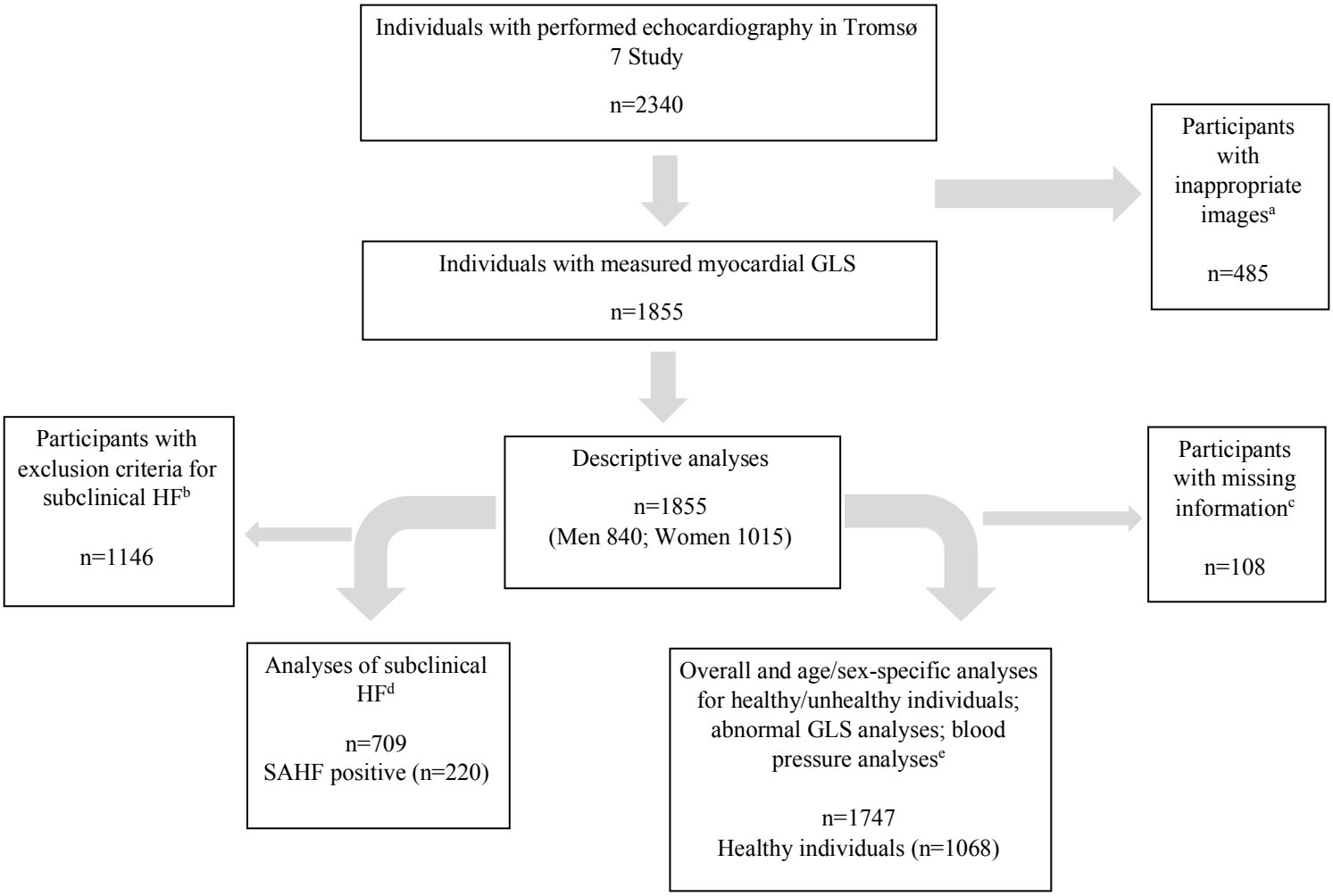
In Paper III we estimated the prevalence of HF in a general population and how HF co-exists with COPD. Using data from the Tromsø 7 survey we chose 1538 individuals (746 men and 792 women) aged 40-84 years with performed spirometry, echocardiography and measured serum Nt-ProBNP levels (Figure 5).

Figure 3. Flowchart of the participants with performed echocardiographic examination (Paper I). The Tromsø Study



[a]Numbers in boxes represent numbers of subjects examined with echocardiography in each wave of the Tromsø Study

Figure 4. Flowchart of the study participants for Paper II. The Tromsø 7 Study (2015-2016)



[a]Participants excluded from GLS analysis due to inappropriate imaging quality.

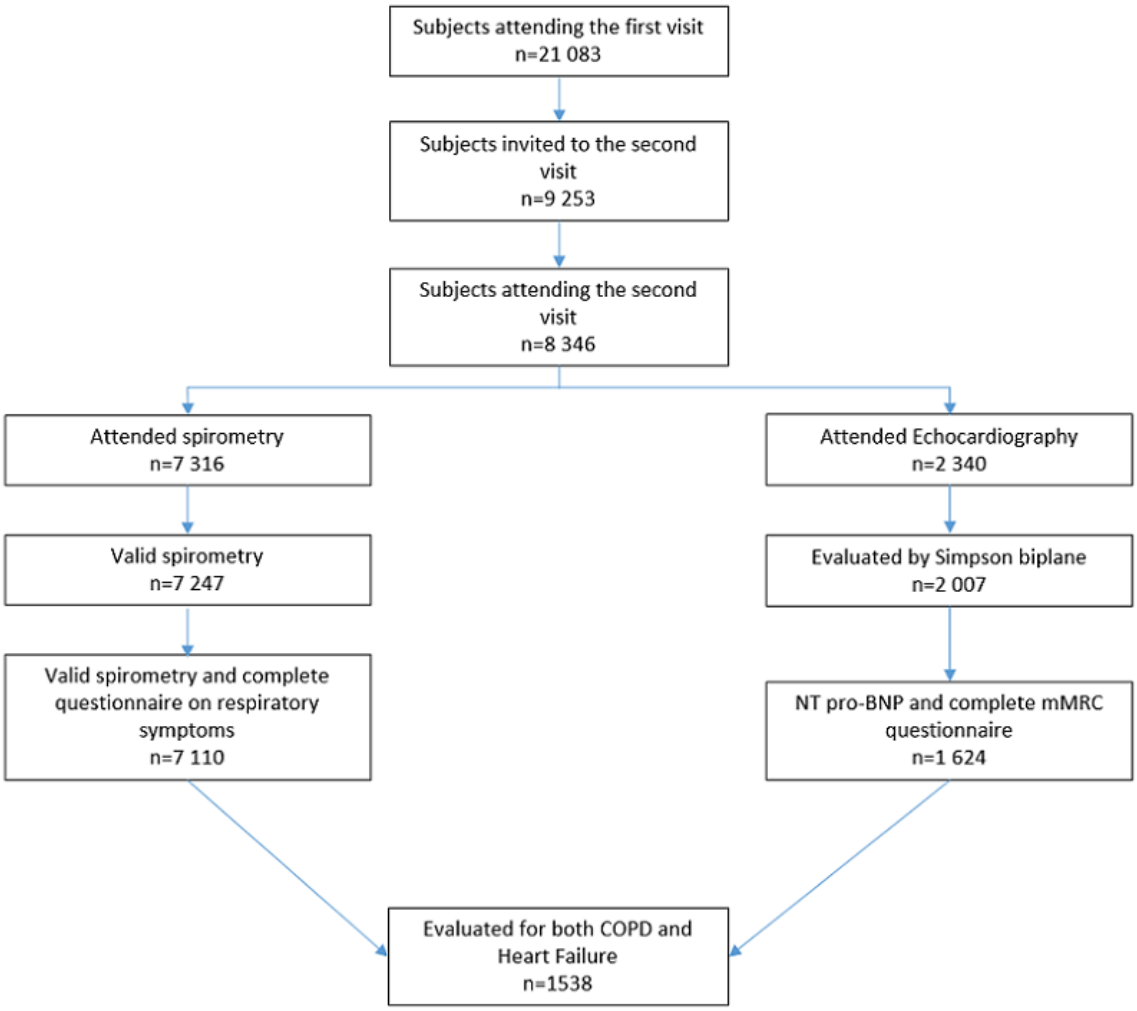
bIndividuals with any of the following: left ventricle geometry abnormalities, left ventricle ejection fraction < 50%, severe valvular heart disease, history of myocardial infarction, heart failure or stroke.

[c]Missing information on any of the following variables: myocardial infarction, angina, stroke, bronchitis, hypertension, diabetes, atrial fibrillation, heart failure, Hb1ac, left ventricle ejection fraction.

[d]Included those with the present at least one of the following: diabetes, metabolic syndrome, obesity, arterial hypertension, angina.

[e]Five individuals with missing information were excluded from GLS analyses according to SBP groups. One individual excluded from logistic regression analysis.

Figure 5. Flowchart of the study participants for Paper III. The Tromsø 7 Study (2015-2016)



[a]COPD: Chronic obstructive pulmonary disease; Nt-proBNP: N-terminal prohormone of brain natriuretic peptide; mMRC: modified Medical Research Council questionnaire.

3.3 Data collection and offline echocardiographic measurements

3.3.1 Self-reported variables and heart failure classifications

Information of traditional risk factors was obtained with the use of self-administered questionnaires. Different information was provided by the first questionnaire depending on survey. In the Tromsø 4-7 surveys information on current smoking (yes/no), current use of antihypertensive treatment (yes/no), history of heart attack (yes/no), MI (yes/no), stroke (yes/no), diabetes (yes/no), COPD (yes/no), asthma (yes/no), atrial fibrillation (yes/no), HF (yes/no), leisure time physical activity (PA) was available.

The NYHA functional classification describes of the severity of symptoms and exercise intolerance in HF. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of HF development. Both classifications are used for evaluation on presence of HF and its severity. While the NYHA classification focused on symptoms of the disease and exercise capacity, the ACCF/AHA stages of HF encompass the development and disease progression, therefore the last one can be used to describe individuals and populations (43). We used ACCF/AHA HF classification in Paper II to elucidate the associations between GLS levels and subclinical HF. The comparison of ACCF/AHA and NYHA classifications are presented in Table 2 (43).

Table 2. Comparison of ACCF/AHA Stages of HF and New York Heart Association (NYHA) functional classifications (43)

ACCF/AHA Stage		NYHA Functional Classification	
Stage A	At high risk for HF but without structural heart disease or symptoms of HF	None	
Stage B	Structural heart disease but without signs or symptoms of HF	Class I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
Stage C	Structural heart disease with prior or current symptoms of HF	Class I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF

		Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
		Class IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
Stage D	Refractory HF requiring specialized interventions	Class IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; HF: heart failure; NYHA: New York Heart Association.

Average physical activity assessment in the Tromsø 4 survey and for individuals aged ≥70 years in the Tromsø 5 survey were different. In order to make the categories in correspondence with other surveys, answers on physical activity were reclassified using an algorithm presented in Table 3 (63).

Table 3. Algorithm for reclassification of physical activity questions from Tromsø 4 and for those aged 70 years or older in Tromsø 5 survey into four levels (63)

Hours of hard weekly physical activity	Hours of light weekly physical activity			
	None	<1	1-2	≥3
None	Sedentary	Moderate	Moderate	Active
<1	Moderate	Moderate	Moderate	Active
1-2	Moderate	Moderate	Active	Active
≥3	Active	Active	Active	Highly Active

In Paper II we have updated the self-reported atrial fibrillation and diabetes variables with its echocardiographic or laboratory confirmation. Thus, in the Tromsø 7 survey we identified individuals experiencing atrial fibrillation during echocardiographic examination who, however, answered "no" regarding atrial fibrillation presence in the questionnaire. These individuals were treated as atrial fibrillation "positive".

Individuals from the Tromsø 7 survey with HbA1c ≥ 6.5% (48 mmol/mL) were treated as having diabetes in addition to those with self-reported diabetes or use of diabetic medication.

Breathlessness in Papers II and III was assessed by the modified UK Medical Research Council (mMRC) breathlessness/dyspnea scale (64) where levels of breathlessness were ranged from 0 to 4. The mMRC scale is presented in the Table 4.

Table 4. The mMRC scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

In Paper I smoking was defined as current smoking (yes/no), in Paper III smoking was defined as never smoked, previous and current smokers.

3.3.2 Physical examination

The blood pressure measurements were made using the Dinamap Vital Signs Monitor 1846 (Critikon Inc, Tampa, Florida, USA) in the Tromsø 3-5 surveys (61), and the Dinamap ProCare 300 (GE Medical Systems Information Technologies, Tampa, Florida, USA) in the Tromsø 6-7 surveys (63, 65). The devices were calibrated during the study at regular intervals. Before the blood pressure control, the upper right arm circumference was measured and the proper cuff size was selected. After the two minutes rest in sitting position the blood pressure measurements were taken three times at 1-minute intervals. The mean value of the last two blood pressure measurements was used (65). We defined hypertension as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or self-reported use of antihypertensive medication.

The body weight was measured with an electronic scale. BMI was defined as weight (kg) to height (m^2) ratio. Individuals with BMI ≥30 kg/m^2 were categorized as obese.

Body surface area (BSA) was calculated by the Du Bois formula (BSA= [$weight^{0.425}$ x $height^{0.725}$] x 0.007184) (66).

Spirometry was assessed with the use of SensorMedics Vmax 20c Encore system (VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA). System calibration was done daily. The procedure was performed according to The American Thoracic Society / European Respiratory Society standards (67). Tests of FEV_1 <0.3 L were treated as invalid (68). Reference thresholds were determined by the Global Lung Function Initiative (GLI 2012) (69).

Atrial oxygen saturation (SpO_2) was measured with a pulse oximeter Onyx II model 9550 (Nonin Medical, Inc., Plymouth, MN, USA) after 15 min of resting period. The highest value among three measurements was registered. Only the values of SpO_2 ≥80% were considered due to uncertain validity of lower values (68).

Lung sound recording was performed using a microphone MKE 2-EW with a wireless system EW 112-P G3-G (Sennheiser electronic GmbH, Wedemark, Germany), placed in the tube of a Littmann Classic II stethoscope (3M, Marplewood MN, USA) at 10 cm from the headpiece. The recordings were stored on computer, which was equipped with custom developed software with recordings labeling function (R700, Logitech Europe S.A., Lausanne, Switzerland). Participants were in the sitting position with the thorax exposed while recording the lung sounds. They were asked to breathe deeper than usual with an open mouth. Recordings were started on inspiration with a duration of 15 seconds with continuing of performing the procedure at six different locations. Two locations between the spine and medial border of the scapula at the level of T4-T5, two locations between the spine and

the mid-axillary line at the level of T9-T10, two locations at the intersection of the mid-clavicular line and second intercostal space (68).

The lung sounds were evaluated by two observers on the first step of assessment. On the second step the third experienced observer was invited to solve any disagreement between the observers in step one. In case of persistent disagreement between observers in the second step, recordings were reclassified and evaluated by two pairs of observers including one junior and one senior lung sound researcher. All of the observers had normal hearing and performed audiometry during experiment. In more than 95% of recordings were agreed by observers from the first step (68).

3.3.3 Laboratory findings

Serum levels of total cholesterol (mmol/L), triglycerides (mmol/L), high density lipoprotein cholesterol (mmol/L), HbA1c (%), Nt-proBNP (pg/mL) and C-Reactive protein were measured according to the previously described procedure (61, 70). Nt-proBNP analyses were performed using electro-chemiluminescence immunoassay (ECLIA) on Cobas e 602 analyser (Roche Diagnostics GmbH, Mannheim, Germany). Reagents were stored at 2-8 °C prior using. The "sandwich procedure" which included incubation, reaction and resulting phases was used for analysis. Calibration was performed at regular intervals and when values went out of defined limits during internal quality control. Internal quality control was performed twice a day. In addition, laboratory took part in external quality control performed by Labquality (www.labquality.fi), with accreditation of Nt-ProBNP values in the 40-35000 pg/mL range. A Nt-proBNP value of 125 pg/mL was considered as normalcy cutoff.

3.3.4 Echocardiography

3.3.4.1 Conventional Echocardiography

Echocardiography was performed by two expert cardiologists using a Vingmed CFM 750 (Vingmed Sound AS, Horten, Norway) ultrasound scanner in Tromsø 4 survey (71). In the Tromsø 5-6 surveys, Acuson Seqoia C258 or C512 scanner (Acuson, Mountain view, CA, USA) were used (72). In the Tromsø 7 survey echocardiography was performed by a qualified sonographer using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. The images were obtained at frequency of 50-70 Hz. Offline image analyses were made using commercially available EchoPac ver. 113 software (GE Vingmed Ultrasound AS, Horten, Norway).

Echocardiographic assessment was done in accordance with ASE and EACVI guidelines (56). The standard imaging planes were obtained in the left lateral decubitus position. LA was measured using the leading edge-to-leading edge convention from the posterior aortic wall to the posterior LA wall. Both the long- and short-axis views perpendicular to the aortic root axis at the level of the aortic sinuses were used. LA diameter was indexed by BSA and presented as cm/m^2.

LV myocardial mass (LVMM) was calculated according to ASE guidelines using the Cube formula:
$LV\ mass = 0.8 \cdot 1.04 \cdot [(IVS + LVID + PWT)^3 - LVID^3] + 0.6g$
Where IVS: Interventricular septum thickness (cm); LVID: Left ventricular internal diameter (cm); PWT: Inferolateral (Posterior) wall thickness (cm). LVMM was indexed by height$^{2.7}$ (LVMMi) and presented as g/m$^{2.7}$ in Papers II and III (56).
LV hypertrophy (LVH) was considered in case of LVMMi >50 g/m$^{2.7}$ in men and >47 g/m$^{2.7}$ in women when indexed by height or LVMMi >115 g/m^2 in men and >95 g/m^2 in women when indexed by BSA (56).

Volumes of the both LA and LV were calculated with biplane Simpson's method. LA volume was indexed by BSA and presented as mL/m^2. LA enlargement (LAE) was defined as LA volume indexed by BSA (LAVi) exceeding 34 mL/m^2 for both sexes.

LVEF expressed in percentage (%) was assessed with biplane Simpson's method from end-diastolic (EDV) and end-systolic (ESV) LV volumes, using the following formula:
$LVEF = (EDV - ESV) / EDV$

Mitral valve Doppler measurements were performed by placing the 2-mm Doppler sample volume between the mitral leaflet tips in the apical 4-chamber view. Spectral gain was adjusted until the flow curve became clear relatively to the background (73). The insonation angle was kept as perpendicular as possible towards the mitral flow. Tissue Doppler (TDI) parameters were derived from apical 4-chamber view with 5 mm sample volume located at the septal and lateral side of the mitral annulus. The following Doppler parameters were studied: peak E (cm/sec) – the mitral peak velocity of early LV filling which was measured at the leading edge of waveform after the electrocardiogram (ECG) T wave; peak A (cm/sec) – the mitral peak velocity of late LV filling which was measured at the leading edge of waveform after the ECG T wave; E/A ratio – peak E velocity divided by peak A velocity; DT (msec) – E wave deceleration time, time interval from peak E-wave along the slope of LV filling extrapolated to zero-velocity baseline; e´ (cm/sec) - pulsed-wave TDI e´ velocity measured as peak modal velocity in early diastole at the leading edge of spectral waveform; E/e´ ratio – peak E velocity divided by mitral annular e´ velocity. An example of the offline measurements listed above is presented in Figure 6.

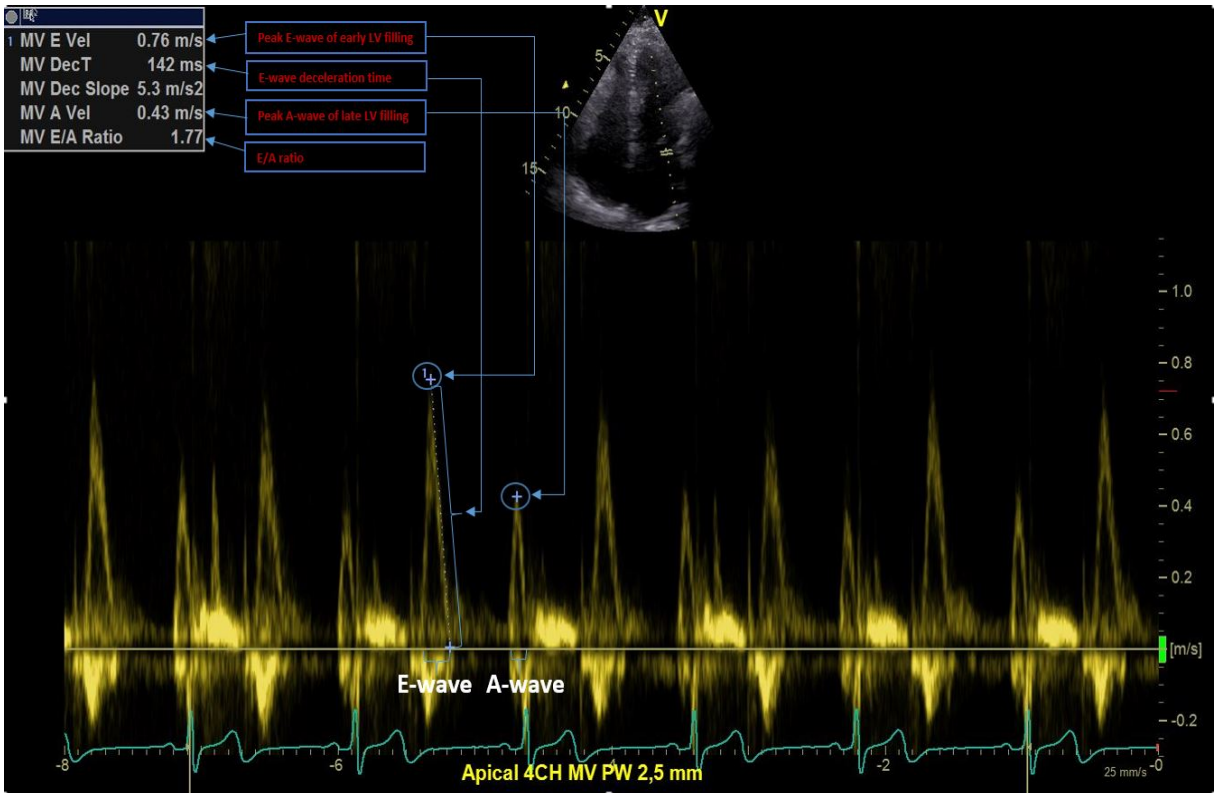
Tricuspid regurgitation flow velocity (m/s) and peak pressure gradient (mm Hg) were assessed with continuous Doppler technique in four-chamber view.

3.3.4.2 Global longitudinal myocardial strain assessment

The analysis of the myocardial GLS was performed with 2D speckle-tracking technique and automated function imaging (AFI) procedure of EchoPac software package. Myocardial GLS values were obtained from averaging of endo- mid- and epicardial layer's GLS from three apical views (4-chamber, 2-chamber and LV apical long-axis view) based on 17-segment model. After automatic tracing of the endo- and epicardial borders images were checked visually for clear visibility of these borders during the entire cardiac cycle. We paid attention to accurate placement of region of interest (ROI) with the aim of avoiding inclusion of extracardiac structures (pericardium) as well as some intracardiac such as papillary muscles, fibrous part of the basal inferoseptum or LV outflow tract. ROI was assessed visually and in case of inappropriate tracking manually adjusted. Views with more than two myocardial segments with inappropriate tracking were excluded from the further analysis. Results of the strain analysis were displayed as a number of strain curves, values of segmental and averaged strain, "bull-eye" image of myocardium which reflects segmental strain. In our study analyses we used the average GLS value. The example of myocardial GLS offline measurements is presented in Figure 7.

Figure 6. Example of the pulse-wave Doppler derived LV filling indices. The Tromsø 7 Study

a. Pulse-wave Doppler derived LV filling indices (Peaks E, A, E/A ratio, DT)



b. Tissue Doppler derived mitral septal peak e`

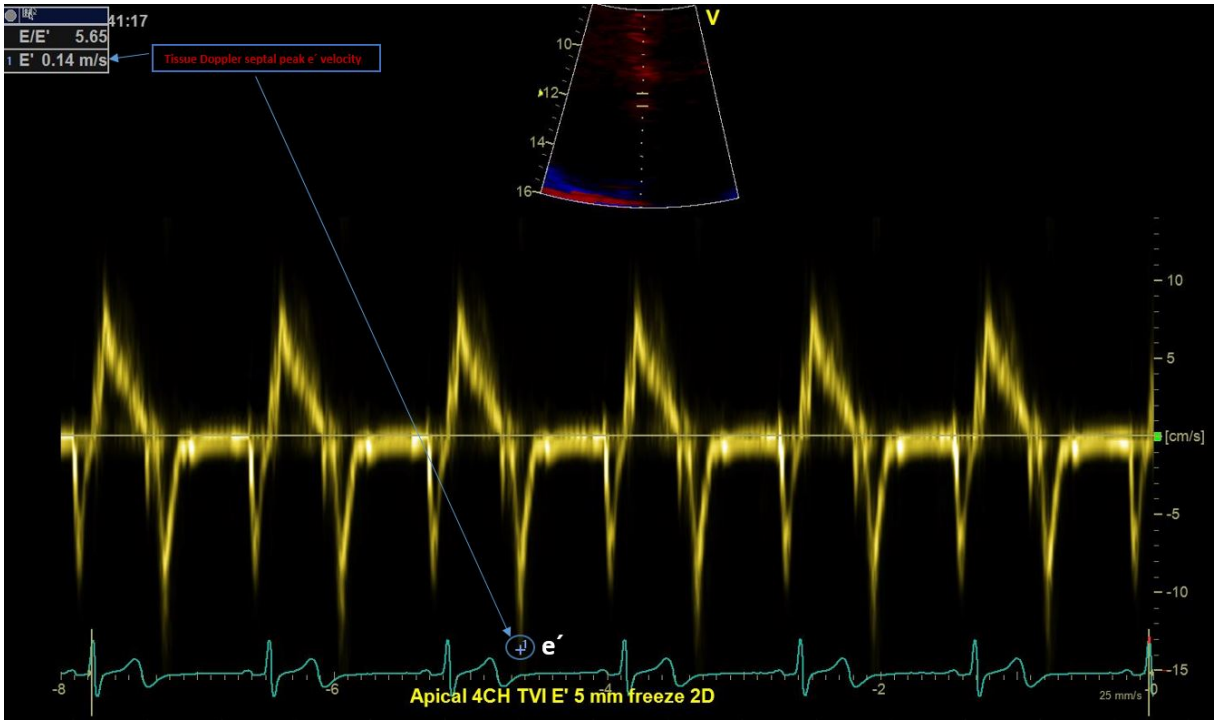
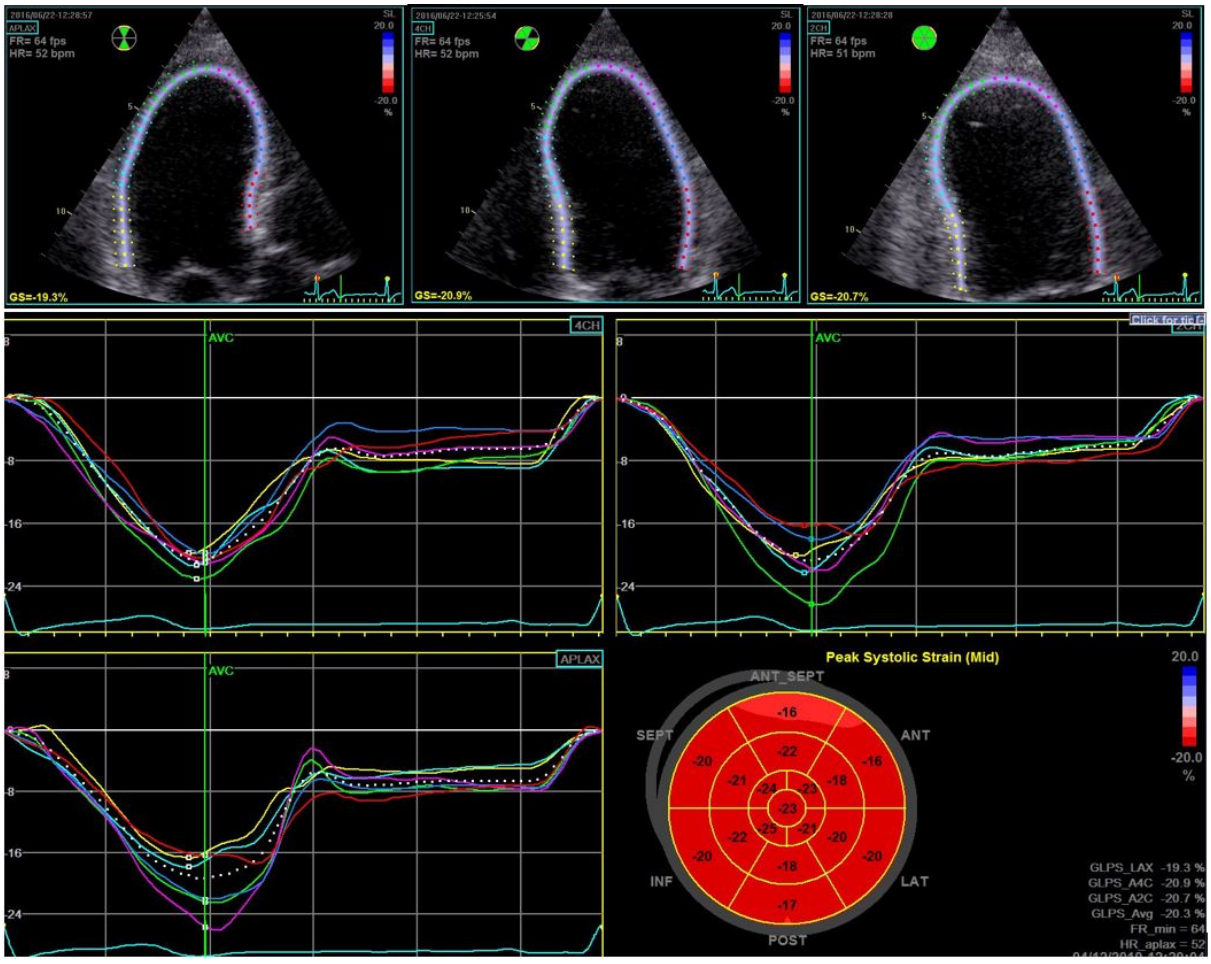


Figure 7. Example of the offline GLS measurements. The Tromsø 7 Study



3.3.5 Composite variables

In Paper I we defined hypertension as a composite variable included both instrumental blood pressure measurements and data from questionnaires of the Tromsø 4-6 surveys. Thus, the individuals were treated as hypertensive if SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or answer "*Currently*" on question "*Do you use blood pressure lowering drugs?*".

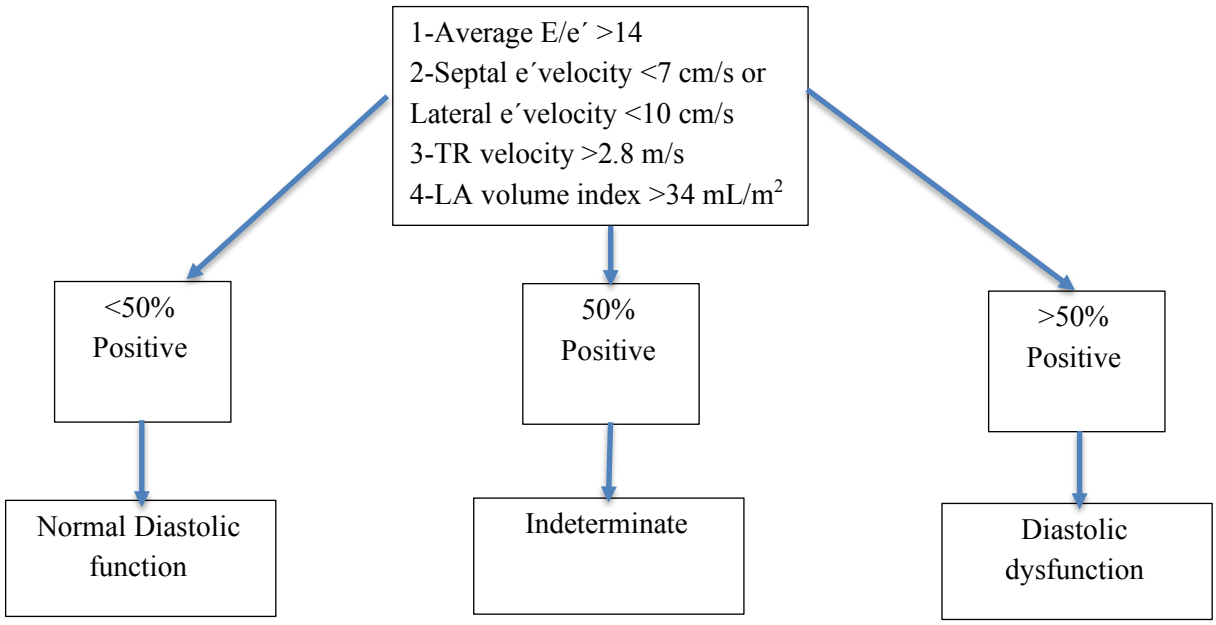
In Paper II based on the Tromsø 7 survey questionnaire the participants were considered as hypertensive if they:

- answered "*Yes, now*" on question "*Have you ever had, or do you have high blood pressure?*";
- and/or had SBP ≥140 mm Hg and/or DBP ≥90 mm Hg;
- and/or answered "*Currently*" or "*Previously, not now*" on question "*Do you use, or have you used blood pressure lowering drugs?*"

HF subtypes we used in Paper III were based on LVEF and defined according to the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF. HF criteria are shown in Table 1.

Diastolic dysfunction was assessed using ASE/EACVI 2016 guideline on recommendations for the evaluation of LV diastolic function by echocardiography (39). Decision tree in Figure 8 shows the algorithm for evaluation of diastolic dysfunction in individuals with normal EF.

Figure 8. Algorithm for evaluation of diastolic dysfunction in individuals with normal EF (39)



E/e´: Ratio of mitral peak E to TDI peak e´; e´: pulsed-wave TDI e´ velocity: TR: tricuspid regurgitation; LA: left atrium.

SAHF assessment in Paper II has been done in two steps. First, we excluded individuals with known CVD (history of MI, HF, stroke), LV geometric abnormalities which include: LV concentric remodelling, LV concentric hypertrophy and LV eccentric hypertrophy (Table 5), LVEF <50% and severe valve dysfunction (mitral and aortic stenosis and regurgitation ≥ grade 3).

Among the remaining individuals we chose those with presence of at least one of the following conditions: diabetes, metabolic syndrome, obesity, arterial hypertension or angina pectoris and identified subjects with SAHF according ACC/AHA guidelines (43).

Metabolic syndrome we used as one of the criterion for defining SAHF was assessed according to AHA/National Heart, Lung and Blood Institute statement (74) with the slight modifications as follows: waist circumference >102 cm in men and >88 cm in women; serum triglycerides >1.70 mmol/l; high density lipoprotein cholesterol <1.04 mmol/L in men and <1.30 mmol/L in women; mean SBP ≥130 mm Hg and mean DBP ≥85 mm Hg.

Table 5. Categorization of LV geometric abnormalities (56)

Relative wall thickness[a]	>0.42	Concentric Remodelling	Concentric Hypertrophy
	≤0.42	Normal Geometry	Eccentric Hypertrophy
		≤47 (women) ≤50 (men)	>47 (women) >50 (men)
		Left ventricular myocardial mass index (LVMMi) ($g/m^{2.7}$)	

[a]Relative wall thickness (RWT) calculated with the formula RWT = (2·PWT)/LVID, where PWT is inferoposterior LV wall thickness, LVID is LV internal diameter at end-diastole

We had data only on non-fasting glucose levels of individuals in the Tromsø 7 survey which cannot be used in current metabolic syndrome definition. Therefore, we used HbA1c as one of the metabolic syndrome criterion. This approach is found to be applicable in clinical settings and according to the

literature HbA1c shows as good predictive ability for metabolic syndrome as fasting glucose does (75).

3.4 Follow-up information

Each person with registered citizenship in Norway has a personal identification number (PIN). With the use of PIN the Tromsø Study participants can be followed up for a wide number of outcomes by linkage of these individuals to national and local registries. In our study the participants were followed up for total death throughout 2016. Information about time of the death was taken from the National Causes of Death Registry which covers individuals living in Norway at the time of the death. The registry includes information about death regardless to the place of death: in Norway or abroad.

An independent endpoint committee validated death cases through retrieving of the available paper medical records (in use until 2001) and digital records afterwards. Information on the study participants who emigrated from Tromsø was obtained through the Population Register of Norway.

In Paper I we followed individuals from the date of attendance of the Tromsø 4 survey until date of death, date of emigration from Norway, or the end of follow-up on December 31, 2016, whichever came first. Of the 2734 individuals aged >50 years who had echocardiography performed at the Tromsø 4 survey, 1399 died during the follow-up period. We treated LV filling indices and LA diameter as time varying covariates in the Cox model. These indices were updated for those participants who did not later meet exclusion criteria (aged <50 years, had atrial fibrillation, had LVEF <50%) and had repeated echocardiography in the Tromsø 5 or 6 surveys. Data on E/e´ ratio was available in the Tromsø 6 survey only, therefore follow-up for this parameter was only 10 years.

3.5 Statistical analysis

All analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA)

3.5.1 Paper I

Descriptive statistics was used for evaluation of baseline characteristics of the study participants. Study participants were categorized by the three levels of LA diameter (<1.5 cm/m^2; 1.5-2.3 cm/m^2; >2.3 cm/m^2), DT (<140 ms; 140-220 ms; >220 ms) and E/A ratio (<0.8; 0.8-1.5; >1.5). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

Time-dependent Cox proportional hazard regression models with fractional polynomials of LA diameter, DT and E/A ratio as predictors were used for revealing the associations between chosen echocardiographic parameters and all-cause mortality. To take into account the changes of the participants baseline information during the follow-up period we updated the baseline information for

those individuals who attended the following surveys. We presented the results for both genders combined because the interaction tests between all of the studied covariates and sex were not significant. The p-value for interaction between sex and LA diameter, DT, E/A ratio and E/e´ were 0.489; 0.696; 0.199 and 0.730, respectively.

The best-fitting fractional polynomials of LA diameter, DT, E/A and E/e´ ratios were chosen while adjusting for sex and fractional polynomials of age using the Akaike information criterion (76). We expected non-linear associations between age and endpoint therefore the hazard ratios (HR) with 95% confidence intervals (CI) were adjusted for sex and fractional polynomials of age. Independent effect of LV filling indices and LA diameter on all-cause mortality was assessed by adjusting the model for SBP, total cholesterol, BMI, smoking, antihypertensive treatment, history of stroke, angina, MI. Association's tests were performed with the use of likelihood ratio test between a model with and a model without fractional polynomial terms of LA diameter, DT, E/A and E/e´ ratios. The proportional hazard assumption was met in all of the models.

We estimated the best cutoff values for LA diameter, DT, E/A ratio using receiver operating characteristic (ROC) curves and areas under the curve (AUC). The optimal cutoff point selection was based on Youden index maximal value (77). For the two latter with a U-shaped relation to risk, ROC curves were estimated for the lower and upper parts separately.

A two-sided $p < 0.05$ was considered statistically significant.

3.5.2 Paper II

We used means with standard deviations and proportions to describe the baseline characteristics of the study participants. Analyses of GLS were sex-specific. Means for myocardial GLS were adjusted for age using linear regression. Absolute means were tabulated for those aged 63 years. We defined the following SBP groups: <120; 120-129; 130-139; 140-159; 160-169; 170-179 and ≥180 mm Hg. Comparison between groups were performed by analysis of variance (ANOVA), χ^2 and Fisher's exact test.

We analysed GLS change by age using weighted linear regression. Lower limit of normal (LLN) myocardial GLS for "healthy" individuals was defined as absolute mean GLS minus 1.96*SD. Bootstrapping with 1000 samples was used for estimation of upper 97.5th and lower 2.5th percentiles for LLN. For assessing the p-value for LLN change by age trend quantile regression models were used. Logistic regression models were applied to estimate odds ratios (OR) for different risk factors of myocardial GLS <LLN. The ORs were estimated separately for each of the following predictors: BMI, history of MI, atrial fibrillation, angina, diabetes, stroke, arterial hypertension and breathlessness scale.

We performed an intra- and inter-reader variability substudy on GLS and presented the results as intra-class correlation coefficients and mean difference ± SD. Coefficient of repeatability (CR) was calculated by formula $CR=2.77 \cdot SD_w$ where SD_w is the within-subject SD. Bland-Altman plots were used for visual assessment of inter-observer variability.

3.5.3 Paper III

The continuous variables were presented as mean with SD. Comparisons between groups were performed with χ^2 test. Age-adjusted logistic regression models were used for OR estimation for different HF and COPD characteristics. Relevant explanatory variables associated with outcome with a p-value <0.1 were included in multivariable model. ROC curves and AUC's were calculated for analysis of COPD prediction and of Nt-proBNP discriminative power in prediction of HF in individuals with history of disease, symptoms and signs. Visual assessment for overlap between COPD, HF and mMRC ≥2 was performed with the use of Venn diagrams.

4 Main Results

4.1 Paper I "Left atrial diameter, left ventricle filling indices, and association with all-cause mortality: Results from the population-based Tromsø Study"

The association between LA diameter and all-cause mortality was U-shaped both in age and sex-adjusted and fully adjusted models. Participants with LA diameter of 1.1 cm/m^2 had a higher risk of death compared with those with LA diameter of 1.8 cm/m^2 (HR = 4.35; 95% CI 1.84-10.30). LA diameter values above 2.1 cm/m^2 characterized with gradual increase of all-cause death risk in age and sex-adjusted model. In the fully adjusted model, risk of death was 4.60 and 5.72 times higher for those with LA diameter of 1.1 and 4.0 cm/m^2, respectively when compared to LA diameter of 1.8 cm/m^2.

U-shaped association between all-cause mortality risk and DT was revealed in the studied population sample. In age and sex-adjusted model, individuals with DT of 80 ms had four times higher risk of death compared with the reference DT value of 155 (HR= 4.65; 95% CI 2.37-9.12). In fully adjusted model HR's for DT of 80 ms and 300 ms were 5.37 (95% CI 2.64-10.94) and 1.44 (95% CI 1.23-1.68), respectively.

E/A ratio showed the same type of association with all-cause mortality risk as LA diameter and DT resulting in HR's of 4.12 (95% CI 2.66-6.40) and 4.50 (95% CI 2.64-7.67), respectively in fully-adjusted model.

Association of E/e` ratio with all-cause mortality risk in age and sex-adjusted model was cubic with 3.48-fold increased risk in those with E/e´ ratio of 25 compared with E/e´ value of 4. While adjusted for additional risk factors, HR became 4.54 (95% CI 1.80-11.44) for the E/e´ ratio value of 25.

We estimated the optimal cutoffs for the parameters listed above. Lower and upper cutoffs for LA diameter were 1.7 and 2.3 cm/m^2, respectively. For DT lower and upper cutoffs were 150 and 200 ms. For E/A ratio the threshold values were 0.6 and 1.2.

In addition, we found no significant advantage of outcome derived cutoffs compared with ASE/EACVI cutoffs in prediction of all-cause mortality. However, the combination of LA diameter and DT or LA diameter + DT + E/A ratio gave the largest AUC of 0.63 for all-cause death outcome. E/A ratio did not add prognostic accuracy to model with all three indices listed above combined.

4.2 Paper II "Global myocardial longitudinal strain in a general population. Associations with blood pressure and subclinical heart failure. The Tromsø Study"

We revealed that myocardial GLS declined with age in men and women in general population sample. In "healthy" individuals mean myocardial GLS (SD) was -15.9 (2.7) % in men and -17.8 (3.1) % in women. "Healthy" women had higher values of myocardial GLS than in men in all age groups. Same as for individuals from general population sample, healthy participants of both genders demonstrated a change of myocardial GLS by age ($p<0.001$).

We defined myocardial GLS LLN as -10.6% for men and -11.7% for women. There was no difference in LLN between age groups revealed in both genders (p-values for age trend were 0.522 and 0.801 for men and women, respectively).

Analysis of the associations between CVD risk factors and GLS < LLN showed that odds of having abnormal myocardial GLS was more pronounced in individuals with diabetes (OR = 2.91; 95% CI 1.52, 5.55), history of angina (OR = 2.68; 95% CI 1.24, 5.80), stroke (OR = 2.67; 95% CI 1.11, 6.43) and MI (OR = 2.47; 95% CI 1.24, 4.96).

Hypertensive women without history of using antihypertensive drugs had their myocardial GLS declined along with SBP increase ($p<0.001$). We did not find significant differences in myocardial GLS in both treated and untreated men of different SBP groups. Linear regression analysis with myocardial GLS as an outcome and 10 mm Hg of SBP as predictor resulted in a 0.2% decrease of myocardial GLS (age and sex-adjusted model). After additional adjustment for BMI, history of: MI, atrial fibrillation, angina, diabetes, stroke, arterial hypertension and breathlessness scale, SBP remained an independent predictor of myocardial GLS decline ($\beta=0.146$; $p<0.001$)

We found that myocardial GLS (SD) was lower in those with SAHF compare to SAHF free individuals (-16.7 (2.5)% vs -17.9 (2.6)%, $p<0.001$).

4.3 Paper III "Prediction of chronic heart failure and COPD in a general population. The Tromsø Study"

A diagnosis of COPD was established in 84 and HF in 139 participants, and 14 had both diagnoses. Age-standardized prevalence of COPD was 5.1% for men and 5.2% for women; the age-standardized prevalence of HF was 6.1% for men and 6.8% for women. The prevalence of the diseases did not differ by sex, but significantly by age ($p<0.001$). A high frequency of FEV_1 <LLN was found in both COPD and HF, and reached 64.3% in subjects with co-existent pathology.

Current smoking predicted COPD with OR 15.8, but was not associated with HF. Value of mMRC ≥2 was a particular strong predictor of HF. As many as 59% of 71 participants with mMRC ≥2 had HF (OR 19.5), while 23.9% had COPD (OR 6.3). Reporting shorter of breath than usual on the examination day predicted both HF and COPD. Basal bilateral inspiratory crackles, was associated with both diseases, but significantly only with COPD, whereas wheezes were a significant predictor of COPD only. Self-reported hypertension, atrial fibrillation, and MI had ORs for HF between 3.2 and 5.4, but did not predict COPD. Among those with an established COPD, approximate one third reported to have the HF, however over-diagnosis was as common as for HF. COPD predicted HF with an OR of 1.97. Nt-proBNP was a strong predictor of HF and not associated with COPD.

In the multivariable analysis, basal bilateral inspiratory crackles became a significant predictor of HF, but not of COPD. When assessing prediction of HF, self-reported HF was excluded, and an AUC of 0.833 (95% CI 0.790 – 0.875) was obtained. Including this variable gave similar ROC-curve (AUC = 0.829). When instead raised levels of Nt-proBNP were included in the analysis, an AUC of 0.909 (95% CI 0.877 – 0.940) was found. Self-reported COPD was excluded when assessing predictors of COPD and an AUC of 0.829 (95% CI 0.783 – 0.875) was found. When the variable was included a slightly higher AUC of 0.840 was found.

5 Discussion

5.1 Methodological considerations

5.1.1 Study design

The Tromsø Study is a prospective, observational, population-based study conducted on general population samples of the municipality of Tromsø (61). The Tromsø Study is the open cohort study. It means that participants can be added or can leave the cohort over time. The possibility of attending more than one study wave for one participant makes the study longitudinal. We handled the advantage of using longitudinal study design over cross-sectional in Paper I where the predictor variables were measured repeatedly giving the possibility to assess the development of these variables over time (78). Thus, we also used the approach of updating the LA size, DT, E/A and E/e´ ratios values while exploring associations between these variables and overall mortality. The long follow-up period of 23 years is also beneficial in exploring the associations of echocardiographic indices with overall mortality in the population (Paper I). Linkage of the Tromsø Study data with the National Causes of Death Registry and Population Register of Norway through the Norwegian PIN ensures the current unique study follow-up of the entire cohort. E/e´ ratio measurements have been conducted first in the Tromsø 6 survey, therefore follow-up period for participants with calculated E/e´ ratio was 10 years. The study cohort was followed from the date of attendance of the Tromsø 4 survey until date of death, date of emigration from Norway, or the end of follow-up on December 31st, 2016, whichever came first (Paper I). Study designs in Paper II and III were cross-sectional, where population data was collected at a single timepoint. The main disadvantage is that only association and not causation can be inferred from a cross-sectional study (79). However, despite the possible disadvantages, the study clearly had the ability to answer the research questions declared in the study aims.

5.1.2 Selection bias and response rate

Bias is any systematic error in epidemiological study that results in incorrect estimate of the true effect of an exposure on the outcome of interest (80). Selection bias occurs when there is a systematic error during the recruitment of the study subjects. Occurrence of the selection bias may lead to non-applicability of the study results to the general population. The possible source of selection bias in the Tromsø Study is non-attendees. The participation rate in the Tromsø Study depending on study wave was >74% in the Tromsø 1-5 with the slight decline in the Tromsø 6 and 7 surveys (66% and 65%, respectively). High participation rates lower the effect of selection bias, however there still might be differences between attendees and non-attendees. Attendees may represent more healthier and more health-concerned group compared to individuals of general population. This effect could be more pronounced in those who attended several studies, due to the healthy survivor bias. Participants disability could possibly lead to selection bias because study participants are obliged to attend the

study site in person. Balancing this bias are persons with early-diagnosed chronic diseases that might be more like to attend the study participants with the aim of getting an extensive examination. The direct comparison of attendees and non-attendees is impossible due to privacy regulations. However, Jacobsen et al. reported a lower mortality rate in attendees at several surveys compared to one time participants (61).

Loss to follow-up is often associated with cohort studies. Bias may occur when participants lost to follow-up differ from persons who remain in the study with respect to exposure and outcome (Paper I). The consequences of loss to follow-up in subjects who had different risks for the outcome is the incidence estimates bias. If the exposure of interest is different due to loss of follow-up then relative measures of association can be biased. Due to linkage of the participant's personal identification numbers to the national and local registries, loss to follow-up considered as minor issue throughout this dissertation. Despite of the fact that there were some losses to follow-up in our study, we do not have a basis to associate these losses with indices of diastolic dysfunction or with all-cause mortality (Paper I). Therefore, subjects remained in the study and those who were lost to follow-up are unlikely to be differential.

5.1.3 Information bias

Information bias results from the systematic differences in the way data on exposure or outcome are obtained from the various study groups (80). Information bias could lead to an incorrect estimate of the association between exposure and outcome. These type of errors in measurements also called misclassifications. It is important to assess which kind of misclassification (differential or non-differential) is present in the study of interest. Differential misclassification happens when the information errors differ between groups therefore non-differential misclassification is considered when the information is incorrect, but is the same across groups. Our study included a long follow-up period of 23 years (Paper I). Long study period is usually beneficial, but slight changes in questionnaires and measuring techniques may occur. Usually the changes in measurement equipment are favorable due to technical progress, however it could affect linear ultrasound measurements from study to study. This could be a potential source of differential misclassification. Echocardiographic data used in Paper II and III was based on the Tromsø 7 study only and one echo-technician collected the images, and one reader performed offline readings of this data. Thus, possible misclassifications associated with echocardiographic measurements in Papers II and III should be considered non-differential. Conducting intra- and interobserver studies on ultrasound data is a proper way of assessing the bias in measurements. Thus, reproducibility of Doppler measurements in the Tromsø 4 survey evaluated in 58 patients by one cardiologist and a doctor trained in echocardiography showed that interobserver mean differences (SD) for mitral peak E, mitral peak A and DT were 0.034 (0.078) m/s, -0.008 (0.091) m/s, and -0.001 (0.034) s, respectively (81). In the Tromsø 5 survey, intraobserver differences on the same echo parameters measured in 40 subjects did not exceeded variation of 10%.

We do not had intra-interobserver study data on the Tromsø 6 survey, however the reliability study using the Tromsø 7 survey data showed intraclass correlation coefficients (ICC) on Doppler indices of 0.90-0.99 in intraobserver study. Interobserver ICC's of 0.84 to 0.98 in the Tromsø 7 survey also showed good to excellent agreement between observers on studied indices of diastolic dysfunction as well on GLS. Therefore, we can presume that bias associated with differences in measurement techniques, software and ultrasound machines are minimized throughout our study.

Another possible source of information bias is the personnel responsible for collecting of ultrasound images. In the Tromsø 4-6 surveys all of the echocardiographic examinations and readings been made online by the same specialist in each survey. It minimized the source of error. Starting with Tromsø 7, ultrasound technician was responsible for patient examination and medical doctor certified in echocardiography made the offline image readings. However, it is very unlikely that a newly-employed echo-technician would gradually distort the quality of collected images and the further reading's results. To ensure quality of the collected images a standard protocol was uploaded on the Vivid machine and followed meticulously. The echo-technician had a one month run in period before the data collection started and had weekly quality assessments by an experienced cardiologist specialized in echocardiography.

Information on risk factors and comorbidities derived from self-administered questionnaires is another source of bias. Self-reported information on smoking, leisure time PA, use of antihypertensive treatment, history of CVD could be misclassified. Study participants could under-or overestimate their level of tobacco consumption, PA level, misreport their status on using medications. However this misclassification unlikely to be differential.

The blood pressure was measured by Dinamap device. We can assume that measures of blood pressure by automatic device were accurate and reproducible (82) as the devices were calibrated before and during each survey.

Another possible source of misclassification is the assessment of diastolic dysfunction (Paper III) with the use of the new EACVI/ASE guidelines (39). The newest classification (2016) which includes four parameters (LAVi, e´ velocity, Tricuspid regurgitation velocity and E/e´ ratio) is reported to have poor concordance ($k=0.18$, $p<0.001$) with the older diastolic dysfunction classification from 2009 (83). Almeida et al. showed that 2016 diastolic function recommendations resulted in lower prevalence of diastolic dysfunction compared with those estimated by 2009 guidelines (1.4% and 38.1% respectively) (83). Authors conclude that among the possible causes of a wide diastolic dysfunction prevalence range is the inclusion of tricuspid regurgitation velocity >2.8 m/s into the new 2016 classification. The proportion of persons with tricuspid regurgitation exceeding the threshold of 2.8

m/s was only 1.2% in the studied population (83). In the Tromsø 7 survey, this proportion reached 1.8%.

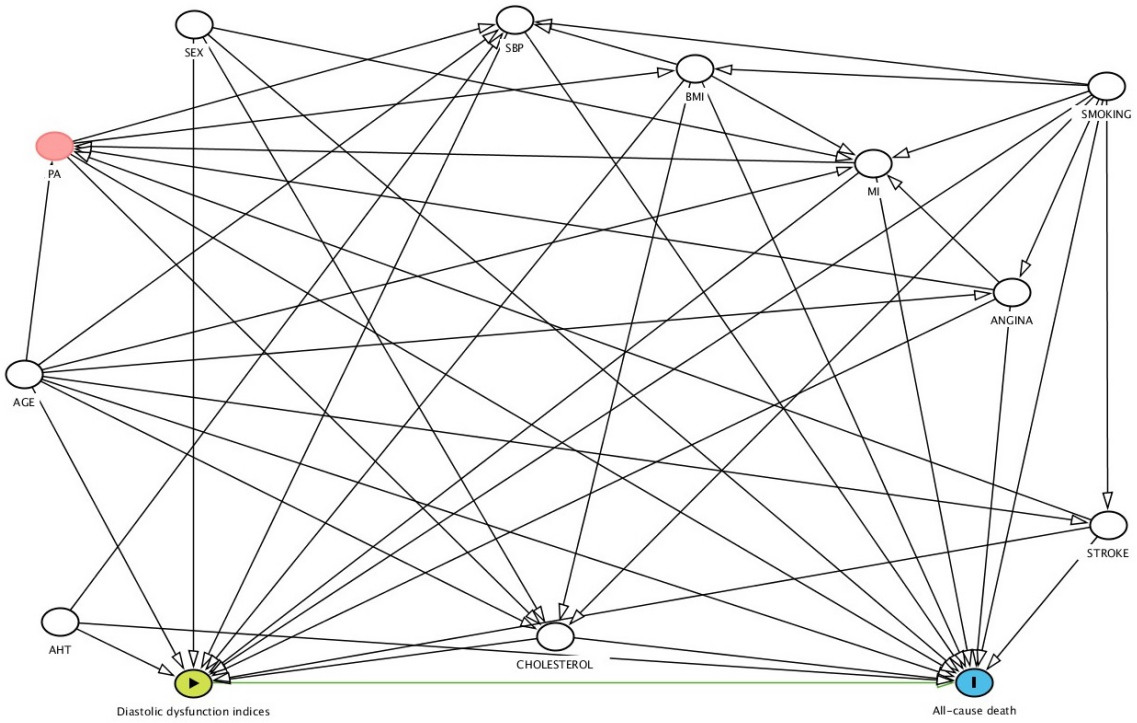
5.1.4 External validity

External validity is the extent to which causal relationships can be generalized to different measures, persons, settings and times (84). Participants of the Tromsø Study were predominantly Caucasians. The criteria used for participants enrollment allowed to conclude that Tromsø Study sample age and sex distribution represents the general adult population of Tromsø (70). Thus, we believe that results of our study are applicable to other northern European populations.

5.1.5 Confounding and interaction

Confounding occurs when an apparently causal relationship between an exposure and an outcome is, in reality, distorted by the effect of a third variable (the confounder) (85). Potentially the associations between indices of diastolic dysfunction (Paper I) and all-cause mortality may be confounded by age, sex, mean SBP, BMI, total cholesterol, stroke, angina, MI, smoking and antihypertensive treatment. Effects of these variables were adjusted in the Cox-regression analyses (Paper I). Age, sex, SBP, BMI and total cholesterol have been reported to be associated with all-cause mortality (86-89). These variables are associated also with indices of diastolic dysfunction (LA size, E/A ratio, DT and E/e` ratio) (90-93). An example of causal diagram describing relationships between indices of diastolic dysfunction and all-cause death used in Paper I is presented in Figure 9. History of angina, MI, stroke has input in all-cause death outcome. Smoking and antihypertensive treatment associations with all-cause death (94, 95) and diastolic dysfunction (96, 97) indices have been demonstrated previously. PA was included as a possible confounder in "Directed acyclic graph" model (98) (Figure 9), however we did not find significant association between PA and diastolic function indices. Therefore, the adjustment for PA in final model was not performed. In Paper III, while estimating the predictors of COPD by logistic regression, adjustment for possible confounders such as age, smoking, mMRC scale ≥2, daily cough in periods, shortness of breath in examination day, crackles, wheezes, self-reported: heart attack, angina, atrial fibrillation, HF, hypertension, diabetes, COPD, asthma; detected HF, FEV_1 <LLN, Nt-proBNP >125 pg/mL, C-reactive protein ≥ mg/L, SpO^2 ≤95% was made.

Figure 9. Directed acyclic graph on association between indices of diastolic function and all-cause death (Paper I) (98)



PA: physical activity; AHT: antihypertensive treatment; SBP: systolic blood pressure; BMI: body mass index; MI: myocardial infarction.

While estimating predictors of HF, adjustments for mMRC scale ≥2, daily cough in periods, shortness of breath on the examination day, basal bilateral inspiratory crackles, self-reported diseases, detected COPD, FEV_1 <LLN and Nt-proBNP >125 pg/mL were made.
It is worth to mention that other characteristics not listed above could be potential confounders. It may be relevant to adjust for LV geometry while testing the associations of abnormal myocardial GLS with different risk factors (Paper II). Thus, Stokke et al. reported LV geometry factors such as wall thickness and/or EDV as confounders while assessing LV systolic function and they may explain reduced strain despite preserved LVEF (99).

Interaction between two independent variables happens if the effect of one of the variables differs depending on the level of the other variable. While interaction occurs, two or more covariates modify their effects on the outcome variable (100). Variables which often interact with other biological parameters are age and sex. In Paper I we found no interaction between sex and LA diameter, DT, E/A and E/e` ratios, therefore results were presented combined for both sexes. In order to limit the influence of age on described markers of diastolic dysfunction and to prevent the potential inaccuracy

of measurements we excluded those aged ≤50 years from analyses. In Paper II we stratified analyses of abnormal GLS by 10-year age groups and sex with the aim to deal with a possible interaction between age, sex and GLS. We found no interaction between age groups and sex in healthy individuals (Paper II).

5.2 Discussion of main results

5.2.1 Left atrial structure and function and all-cause mortality

We used various echocardiographic markers of diastolic function such as LA size, DT, E/A and E/e´ ratios for prediction of all-cause mortality risk and obtained U-shaped relationship between described parameters (LA size, DT, E/A ratio) and cubic association of E/e´ ratio with all-cause death outcome.

Results of our study are in line with previous reports on the role of LA size as significant prognosticator of all-cause (101, 102) and CVD mortality (103, 104). The role of enlarged LA size in prognosis was intensively explored the last decades, however data on small LA function is sparse, despite of the growing interest to its prognostic value. To our knowledge, the comprehensive analysis of all-cause death in individuals with small LA during the long follow-up had not been elucidated. However, it is worthwhile to mention some reports on small LA and its association with various outcomes. Thus, increased mortality risk in patients with acute pulmonary embolism was found by Aviram et al. (105). Rosenbaum et al. found small atria to be independent predictor of all-cause death in patients undergoing pulmonary angiography (106). The same group of authors in year 2019 showed independent association of small LA (LAVi <16 mL/m^2) with poor short and long-term mortality on cohort of 17343 hospitalized patients with median follow-up of 2.4 years (107). Aetilogy of a small LA is different than in normal and enlarged atria and includes decreased intravascular volume, pulmonary hypertension with under-filling of the LA, pericardial and pleural effusions, right ventricle failure and left to right shunt (107). Around 20% of patients had their small LA aetilogy undetermined (107). In our study sample 11 of 24 individuals (45.8%) with LA size <1.5 cm/m^2 died during follow-up. Unfortunately, we were not able to assess the cause of death of all studied individuals, however MI as cause of death was established in only one of them. Rozenbaum et al. showed that individuals with small LA had less CVD risk factors but higher prevalence of malignancies (107). We can presume that in our sample the cause of death distribution could be nearly the same as in Rozenbaum et. al. study. Pathophysiological background of associations between all-cause death and small LA size was not properly studied, however some authors consider decreasing LA emptying fraction as an independent predictor of mortality (108). Despite the fact that individuals with small LA according our data had 1.20-4.35 times increased risk of all-cause death, the full pathophysiological mechanisms of mentioned associations are yet to be explored.

Mitral peak E DT is considered as one of the important parameters of LV filling and independent predictor of adverse events. In our study a U-shaped pattern of DT association with all-cause death in general population sample was revealed. Results of the Strong Heart Study showed the same type of relationship with CVD outcomes where shorter and longer DT being associated with worse prognosis (109). Pathophysiological basis for heart functional impairment when DT has extreme high or low values is most likely the LV stiffening (short DT) or impaired LV relaxation (long DT), conditions

which lead to progression of diastolic dysfunction and HFpEF. While assessing optimal cutoff values for DT and all-cause death risk we were in line with the previous report of Morales et al. where patients with DT <130 ms had lower event-free survival during 21-month follow-up compared with those with intermediate and highest DT tertile (110). Authors conclude that 130 ms threshold is allowed for prediction of high-risk subgroup of patients independently of their NYHA functional class (110). Peltier et al. showed that short DT in patients with LV systolic dysfunction is an independent predictor of poor prognosis both in sinus rhythm and in atrial fibrillation (111). Our results suggest that the DT lower cutoff point of 130 ms could be applied also in a general population. Contrary to Morales et al. we found that individuals with DT >185 ms had a gradually increased risk of all-cause death outcome. One of the possible reasons for discrepancies between results could be the longer follow-up period of our study.

E/A ratio analysis in our study showed that its values exceeding the range of 0.8-1.4 are associated with increased hazard of all-cause mortality. Normal E/A values were defined as 0.8-1.5 in ASE (EACVI) 2009 guidelines (38). Later in 2016 guidelines on evaluation of diastolic function, E/A ratio assessment was recommended for in individuals with reduced EF in order to evaluate elevated LA pressure. The upper value of E/A ≥2 is considered as threshold for grade III diastolic dysfunction with restrictive LV filling pattern (39). According to our results, the specificity of upper E/A cutoff of 1.2 based on Youden index estimation was lower than ASE/EACVI recommended cutoff of 1.5 (46% vs 59% respectively) which makes recent guideline-recommended values of E/A preferable for ruling in persons at risk of all-cause death. The common issue of E/A ratios derived from offline echo readings is a underestimation of E/A abnormalities due to occurrence of pseudonormal LV filling. In our study (Paper I) the E/A pseudonormalisation wasn't considered, however we excluded individuals with severe LV dysfunction (LV EF <50%) and atrial fibrillation from analyses of all-cause mortality with the aim to minimize possible influence of pseudonormalization.

E/e' ratio is a measurement index for prediction of LV filling pressures (39). Along with LV filling pressure estimation, our findings showed that E/e' is also a good prognosticator of all-cause death outcome in general population. These results are in contrast with previous research of Mogelvang et al. where no association between all-cause mortality and E/e´ratio was found (112). Borderline associations of E/e´ratio and risk of cardiac events was showed by Kuznetsova et al. (113). Prasad et al. had recently demonstrated an association of E/e´ratio with all-cause death in univariable model in patients with LV EF >35% and first-ever MI (114). However, multivariable analysis did not show an independent effect of E/e´ratio on all-cause death outcome (114). It is worth to mention that some studies revealed an increased all-cause mortality in specific group of patients. Thus, Park et al. demonstrated that patients with normal LV EF and non-valvular atrial fibrillation and E/e´>15 had worse survival rates than those with E/e´≤15 (115). In acute HF E/e´was an independent predictor of all-cause mortality (116). In Paper I we used septal e´ for analysis of E/e´ ratio associations with all-

cause death. Up to date, there is no clear consensus on choosing sites of e´ measurements. The diversity of E/e` is associated with measuring site and individual variations, therefore it is not clear whether E/e' should be obtained from septal, lateral or both sites if available. However, a recent publication of Wang et al. showed that septal and lateral E/e´ ratios were equally useful in predicting cardiac events in a general population (40). Based on literature data we assume that using the septal E/e´ in longitudinal analysis is applicable for all-cause mortality prediction.

In our research, we were interested in verifying the ability of outcome-derived reference values of LA size and LV filling indices to predict all-cause death outcome better than ASE and EACVI recommended thresholds. The basis for our assumption went out from other well described in literature examples of discordance between normal values derived from statistical distribution and outcome-derived cutoff points. Thus, normal estimated age-specific reference ranges for cholesterol in population of Northern Norway are 2.9-6.1 mmol/L, 3.3-6.9 mmol/L and 3.9-7.8 mmol/L for those aged 18-29, 30-49 and ≥50 years, respectively (117). The demonstrated upper cholesterol values are substantially higher than those proposed in guidelines for CVD risk prediction models (118). In our study the outcome-derived model which combined LA diameter, DT and E/A ratio showed the same discriminative power for prediction of all-cause death (AUC=0.63, $p < 0.001$) as a model with ASE and EACVI cutoffs. Despite that the studied model did not show a better predictive ability in comparison with an existing one, we assessed the incremental power of each index of the LV filling parameters and found that E/A ratio did not add prognostic accuracy in models where LA diameter and DT were already included. Interestingly the predictive ability of E/e' ratio for all-cause death was not superior compared with LA diameter, E/A ratio and DT. Therefore, using of "old" indices of diastolic dysfunction could be relevant in clinical settings when tissue Doppler data is unavailable.

5.2.2 Global longitudinal myocardial strain. Normal values, association with systolic blood pressure, subtle cardiac impairment and heart failure

GLS as a parameter of myocardial deformation is widely used in research of cardiac function in normal conditions and pathology. This semi-automatic, reproducible and novel speckle-tracking based technique showed ability to detect early subclinical impairments of heart function, therefore the interest to GLS among cardiologists and general practitioners is growing. In Paper II we tried to emphasize the importance of GLS evaluation in general population and assess factors influencing GLS.

However, the first issue we faced with in our study was the understanding of what values of GLS could be considered as "normal" and what range of GLS values one should expect in healthy individual. To date no consensus has been reached on normal GLS cutoff point, however GLS of -20% is expected as normal in healthy subjects according the latest guidelines (56). The vast body of literature devoted to the normal values of GLS unfortunately yielded diverse results, which makes difficult to standardize GLS for its further use in clinical settings. Thus, Takigiku et al. reported GLS (SD) values of -21.3 (2.1)%, -18.9 (2.5)% and -19.9 (2.4)% respectively depending on vendor. Study sample represented of 817 healthy individuals aged 0-88 years (119). Meta-analysis published in 2013 included 24 studies on GLS (57). Authors found mean GLS level between -15.9% to -22.1% (mean, -19.7%; 95%CI -20.4%, -18.9%). Main variations among different GLS ranges were likely to be associated with differences of SBP (57). Data gathered from Korean population-based sample (n=501) on adult subjects aged 20-79 years showed GLS (SD) level of -20.4 (2.2)% (95%CI -25.4%, -16.7%). The higher values of GLS were in women, however authors did not find significant differences in GLS between age groups (120). Another research of Nagata et al. on normal range of myocardial layer-specific strain among 254 healthy subjects considered the value of global endocardial LS of -23.1 (2.3)%, transmural LS of -17.6 (1.9) and epicardial LS of -17.6 (1.9)% (60). Study results does not provide the total mean value of GLS however with respect to layer-specific values it can be presumed as approximate value of -20%. Likewise Park et al. (120) Nagata et al. reported no significant trend on GLS change by age, but significant effect of female sex in increase of GLS values (60). Alcidi et al. in single-centre study on 266 healthy subjects showed slightly higher layer-specific myocardial strain values than Nagata et al. with independent effect of ageing on strain (121).

In our general population sample mean myocardial GLS (SD) in 1068 healthy participants was -15.9 (2.7)% in men and -17.8 (3.1)% in women with significant change of GLS by age. These findings are in line with Dalen et al. report who gathered GLS (SD) values of -15.9 (2.3)% in healthy men and -17.4 (2.3)% in women studying 1266 healthy Norwegian individuals (59). The values we obtained were lower than those described in the general literature and we assume several possible causes being

relevant for this. Among these causes are the following: differences in “healthy individual” definition, myocardial layer chosen for calculating GLS, software and vendor diversity.

We tried to include all available questionnaire-based risk factors and health conditions, which could influence strain, therefore we assume our “healthy” definition could be different than ones used in previous studies. Thus, some studies refer only to hypertension and diabetes as exclusion criteria (120), others do not include individuals with atrial fibrillation and COPD (119, 121), some of the studies include additional criteria like chronic kidney disease (60).

In our study we used averaged values of GLS derived from three modalities (apical long-axis, two-chamber and four-chamber views) and from endo- mid- and epicardial layer from each view. Therefore we suppose that the influence of including or excluding epicardial GLS which is according to the literature data is approximately 30% lower than endocardial GLS (60) could be significant cause of difference between studies reporting different normal values for overall GLS.

Software version used for offline reading procedures could also influence GLS. It is difficult to assess the possible grade of the deviations regarding software versions, however some authors report significant changes of GLS values after upgrading of speckle-tracking software (122). The type of GLS deriving method e.g. by two- or by three-dimensional echocardiography should also be mentioned. The latest meta-analysis on normal ranges of LV strain by three-dimensional speckle-tracking reported normal mean values of GLS from -15.80% to -23.40% with the mean of -19.05% (95%CI -18.18%, -19.93%) along with consistent association of GLS with software differences (p=0.016) (58). Vendor-specific image postprocessing algorithms is one of the cornerstone issues which suppresses the clinical use of strain imaging (119). From the early use of strain imaging some authors aimed to assess quality and reproducibility of strain measurements made on different platforms and software. Thus, Manovel et al. in 2009 found that myocardial strain measurements made on platforms of two widely used vendors (GE Healthcare and Toshiba Medical Systems) are comparable when qualifying LV function (123). Contrary in 2015 Nagata et. al reported that vendor-independent 2D strain software showed moderate correlations between GLS in the same individuals (124). After launching a task force by EACVI and ASE with the aim of determining variability in speckle-tracking measurements, safe use of GLS in clinical practice was concluded (125). Further implementation of principles declared in standardization initiative resulted in substantial decline of GLS variability between vendors (126).

Along with sex-specific mean GLS values we assessed sex and age-specific GLS LLN which non-significantly declined by age in both sexes. The values of LLN we obtained (-10.7% 95%CI: -11.2%, -10.2% in men and -11.7% 95%CI: -12.2%, -11.2% in women) were lower than those showed in

D'Elia et al. meta-analysis where GLS value -18.2% was proposed as LLN for measurements made with use of GE platform (127). We assume that differences in LLN could be partly explained by its definition. In our study we used mean-2SD as a threshold for LLN while D'Elia refer to 5th percentile which could probably give higher absolute GLS normalcy cutoff. Applying the 5th percentile cutoff on our study population we obtained slightly higher values of GLS LLN in healthy individuals (-11.4% for men and -12.4% for women) as expected.

The logistic regression analysis on risk factors associated with abnormal GLS showed that odds of having abnormal GLS are common for most of the CVD risk factors in age and sex-adjusted models, which was revealed in earlier studies (128). We calculated sex and age-specific ORs for each risk factor separately and have not applied multivariable model in order to avoid the table 2 fallacy (129). Presenting multiple adjusted effect estimates from a single model can lead to mistaken interpretations of the estimates as covariates can have different confounders/effect modifiers/intermediate factors/colliders and the interpretation of a confounder effect estimate may be different than for the exposure effect estimate.

The association between GLS and SBP became our object of interest due to growing number of individuals suffering from hypertension and its complications along with link between LV overload and impairments of myocardial mechanics. Lee et al. demonstrated prognostic importance of impaired GLS in hypertensives (130). However, the association between hypertension and GLS reduction is not yet clear. Some authors reported association of afterload with GLS (131) while others considered low-effect of afterload on LV motion abnormalities (132). In patients with HF, afterload fluctuations in a stable clinical condition were not associated with unstable LV longitudinal deformation over time (133). It is unclear whether afterload influences on GLS reduction alone or GLS impairments are associated with subendocardial ischemia and myocardial fibrosis (134). Most likely the GLS magnitude is a result of interplay between loading conditions and myocardial determinants: myocardial fiber's orientation, passive tissue behavior, crossover between myocardial layers and direction of active stress in relation to the fiber's orientation (135). Results of our study showed the decline of GLS both in men and women by increasing SBP, however this trend was non-significant in men mostly due to limited number of men in the older age group. An interesting finding is that GLS already declines in a general population sample in individuals with SBP of 130-139 mmHg reflecting the early impairments of heart mechanics.

With the current predominance of HFpEF phenotype in general population the prediction of future adverse events is a promising strategy in CVD prevention. As it was earlier established, GLS was found as important predictor of outcome, stronger and more reliable than LV EF especially in individuals with preserved systolic function (136). The benefits of using GLS as a risk assessment tool

was shown in all stages of HF (136). A number of studies have shown the prognostic importance of GLS assessment in general population (137-139). Our findings of a significant difference in GLS (-16.7% vs -17.9%) between persons with/without SAHF in general population, confirm the usefulness of the SAHF criteria of detecting a high-risk group in need of screening for possible prophylactic interventions.

5.2.3 Prediction of chronic heart failure and chronic obstructive pulmonary disease in general population

HF and COPD are known as the diseases with high morbidity and mortality (1, 140). Negative economic consequences as result of HF and COPD raise challenges for health authorities, researchers and medical practitioners. Despite of being curable diseases, HF and COPD are often late- or misdiagnosed especially when two pathologies are co-existing.

The causes of being underdiagnosed with early stages of HF and COPD are: non-specific early symptoms of exertion dyspnea, cough, crackles and wheezes which often overlap between two pathologies. The consequences of the issues highlighted above are the delay in diagnosis and wrong treatment strategies for affected group of patients (141).

In Paper III we aimed to study the prevalence of HF and COPD, extent of overlapping of HF and COPD in general population and factors which may predict both diagnoses. We assessed how precisely current guidelines predict HF and COPD and described prognostic value of Nt-proBNP.

The age-standardized prevalence of HF in our study reached 6.1% in men and 6.8% in women. These proportions were quite higher than in was earlier reported in literature. Thus, data from population based Swedish cohort study showed age-adjusted prevalence of HF of 1.5-2% (142). However, all HF diagnoses in our study were validated by echocardiography while Lindmark et al. reported about 40% echocardiographic coverage of study population (142). Nielsen et al. showed nearly similar distribution of HF subtypes as we found in our study especially for HFpEF (37% in Nielsen et al. vs 40% in our study, respectively) (46). Interestingly, only 17% of those where HF was verified by echocardiography and laboratory findings were aware of their diagnosis. We can presume that change of HF classification in 2015, which includes now also levels of serum Nt-proBNP, structural abnormalities of LV or LA and diastolic dysfunction may be one sources of misdiagnosis.

In comparison with the HUNT study (143) where age-adjusted prevalence of COPD was 7.3% we obtained lower COPD prevalence of 5.1% and 5.2% for men and women, respectively. Partly it could be explained by differences in diagnostic classifications used in both studies. We used respiratory

symptoms as one of the diagnostic criteria which may influence the prevalence. It is worth to mention that population sample in the HUNT study was represented by younger individuals and higher smoking prevalence compared with the Tromsø 7 survey. The issue of choosing the FEV_1 cutoff for COPD definition has been widely described in literature. Nowadays the definition of COPD provided by GOLD includes FEV_1 as one of criteria with a threshold of 0.7 (144). However, this definition was criticized due to presence of physiological limitation of the airflow, decline of FEV_1/FVC ratio in elderly individuals and following overestimation of COPD prevalence in older age groups (145). To our view, other approach which deals with age- and height-adapted FEV_1 LLN as cutoff point for COPD diagnosis seems to be more relevant with respect to our study sample as the proportion of individuals aged 60 years or more is exceeding 65%. However, it is worth to mention that LLN approach is limited by fixation of COPD prevalence on 5% level across age-groups in community settings, reduced reproducibility and obtaining of not post- but prebronchodilator FEV_1 values which may induce misclassification of those with positive reversibility test (145).

The presence of both COPD and HF was revealed in 14 participants. We found that the proportion of HF in those with COPD was 16.7% and lower than reported in previous studies (146). In patients with HF comorbid COPD occurred in 10% of individuals. Iversen et al. showed that 35% of patients admitted with HF had COPD. We assume that these differences mainly are due to a difference between acutely ill patients and a general population sample, but could also to some extent be explained by choosing 0.7 FEV_1 cutoff instead of FEV_1 LLN in COPD definition.

Predictors of HF and COPD in general population were evaluated in our study. Among the strongest predictors of HF was shortness of breath. The importance of shortness of breath evaluation was shown in acute clinical settings (147, 148). The predominance of shortness of breath was revealed also in previous research by Fonseca et al. (149). Basal crackles had good discriminative power for predicting HF along with history of MI, leg oedema and Nt-proBNP. The presence of wheezes was independent predictor of COPD. We made a sensitivity analysis on expanded sample of 7110 subjects and found the enhancing of associations of crackles and wheezes but not Nt-proBNP with COPD which highlights the importance of auscultative signs in clinical settings.

Overall predictive ability of symptoms, signs and history of previous diseases was high both for HF and COPD and adding of Nt-proBNP to our model increased the AUC up till 0.91 strongly supporting use of this predictive approach with Nt-proBNP in clinical settings.

6 Conclusions

1. Our study concludes that a wide span of LA diameter, DT, E/A and E/e´ ratios values are associated with increased all-cause mortality risk. The predictive ability of outcome-derived diastolic dysfunction indices was similar to ASE and EACVI cutoff points for all-cause death prediction. The combination of LA diameter with DT in all-cause death prediction model had best discrimination power while E/A ratio did not add incremental value.

2. Peak myocardial GLS showed a declining trend in both sexes in both the total population and in healthy individuals. An increase of SBP in a general population was associated with GLS decline in women. The majority of CVD risk factors contributed in subtle impairments of myocardial function measured as a decrease in GLS. Subclinical HF of early stage was characterized by decreased GLS.

3. Overlap between HF and COPD in a general population sample was found in 9.2% individuals. History of disease, symptoms and signs remain crucial factors for differential diagnosis between HF and COPD. Wheezes are independent predictors of COPD, Nt-proBNP is independent predictor for HF. Echocardiography and spirometry are the main instrumental methods that are needed for verification of diagnoses.

7 Implications of results and future research

The study results may be used as prognostic tool in clinical settings. LA size and diastolic dysfunction indices appear to be good prognosticators in persons with HFpEF for various adverse outcomes as all-cause and CVD mortality. Results of our study highlight an issue of risk of death in persons with small atria, individuals which are usually out of coverage of general practitioners. Different prognostic models of all-cause mortality and use of particular indices of diastolic dysfunction may help echocardiographers, researchers and clinicians to identify and follow individuals at risk.

Assessing the GLS values in general population helps to get overview on prevalence of subtle myocardial impairments. Associations of GLS with CVD risk factors and HF we have found strengthens role of GLS as precise and reproducible diagnostic method which may be used both in population screenings and assessing of individual signs of early myocardial dysfunction.

Finally, data on COPD and HF and their relationships in general population may help general practitioners to choose more reliable and precise algorithm for differential diagnosis between two pathologies and therefore prevent cases of misdiagnosis and implying of wrong treatment strategies.

If the recent HF prevalence trends will continue one can expect the increased burden on healthcare system next decades. In these circumstances the identification of persons at risk of developing HF and especially HFpEF will became priority among prevention strategies. The main components of diastolic dysfunction assessment (LA size, transmitral flow parameters, TDI indices of LV relaxation) remain the same during the last years and adding the novel methods as LV and LA strain could facilitate the diagnosis (150).

Unfortunately, LA strain was not measured in the Tromsø 7, however it could be made in future studies using stored cine loops. It would be also interesting to analyze indices of diastolic dysfunction especially E/e´ratio not only at rest but during the physical exertion which is considered as more precise evaluation of LV filling pressures.

The recording of all necessary parameters to define HF according to the new guidelines in Tromsø 7 will soon enable endpoint validation the new definition of diastolic dysfunction and enable comparison with the older indices of diastolic dysfunction validated in Paper I.

The rich data gathered over time will generate further studies on the risk of clinical valvular heart disease for minor regurgitations, change in the prevalence of diastolic dysfunction and systolic dysfunction over time in a general population with a rapidly changing incidence of coronary heart disease and declining risk factor levels. The added value of GLS in subsequent risk of non-fatal or fatal CVD can also be determined based on the collected echocardiographic data.

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Paper I

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WILEY Echocardiography

Left atrial diameter, left ventricle filling indices, and association with all-cause mortality: Results from the population-based Tromsø Study

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Aims: To examine the associations between diastolic dysfunction indices and long-term risk of all-cause mortality in adults over 23-year follow-up.

Methods and results: Participants (n = 2734) of the population-based Tromsø Study of Norway had echocardiography in 1994–1995. Of these 67% were repeated in 2001 and/or 2007–2008. Mortality between 1994 and 2016 was determined by linkage to the national death registry. Cox regression was used to model the hazard of all-cause mortality in relation to left atrial parameters (treated as time-dependent using repeated measurements) adjusted for traditional risk factors and cardiovascular disease. During the follow-up, 1399 participants died. Indexed left atrial diameter, mitral peak E deceleration time, and mitral peak E to peak A ratio showed an U-shaped association with all-cause mortality. Combining left atrial diameter with mitral peak E deceleration time increased the prognostic accuracy for all-cause mortality whereas adding mitral peak E to peak A ratio did not increase prognostic value. We estimated new optimal cutoff values of left atrial diameter, mitral peak E deceleration time, and mitral peak E to peak A ratio for all-cause mortality outcome. E/e′ had a cubic relation to mortality.

Conclusion: Both enlarged and small left atrial diameters were associated with increased all-cause mortality risk. A combination of Doppler-based left ventricle filling parameters had an incremental effect on all-cause mortality risk. The cutoff values of diastolic dysfunction indices we determined had similar all-cause mortality prediction ability as those recommended by American Association of Echocardiography and European Association of Cardiovascular Imaging.

KEYWORDS
all-cause mortality, diastolic dysfunction, echocardiography, epidemiology, left atrial diameter, prognosis

1 | INTRODUCTION

Heart failure (HF) is associated with reduced quality of life and premature mortality.[1] It is defined as a clinical syndrome associated with a wide range of left ventricular (LV) structural and functional abnormalities of different underlying etiologies.[2] Recent data suggest that the incidence of HF with reduced LV ejection fraction (HFrEF) and HF with mid-range LV ejection fraction (HFmrEF) is decreasing while incidence of HF with preserved LV ejection fraction (HFpEF) is increasing.[1]

Detection of asymptomatic diastolic dysfunction is a strong risk factor for developing HFpEF.[3] Left atrial (LA) diameter measured in M-mode and mitral flow measurements such as the ratio of the maximal E wave to the maximal A wave (E/A ratio) and the deceleration time of the E wave (DT) has been commonly used as indices of diastolic dysfunction. Enlarged LA diameter is a significant predictor of adverse cardiovascular events.[4] Additionally, LA enlargement has been found to be an independent predictor of HF development, atrial fibrillation, coronary heart disease, stroke, and all-cause mortality.[5–8]

A short as well as long DT is associated with poor cardiovascular outcomes.[9] E/A ratio is used for evaluating filling pressure and degree of diastolic dysfunction and also provides prognostic information.[10]

The number of studies on the diagnostic impact of LA size and function through the last decades indicates its importance for cardiovascular health.[11] However, there is a lack of data on associations between lower ranges of LA size and all-cause mortality rates. The American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) has put forward a series of LA diameter cutoffs that are defined purely in terms of percentiles of the distribution. Their ability to predict mortality has not so far been ascertained.[12]

The recent ASE and EACVI guidelines define diastolic dysfunction in terms of a combination of statistically "normal" values of mitral flow indices derived from a small sample of healthy individuals and predictions of mortality by LA diameter from a surveys of the general population.[13] These guidelines have not validated the combination of these indices as predictors of disease development or mortality.[10,13] In the latest guidelines septal and lateral e′ peaks, average E/e′ ratio, LA volume index, and peak tricuspid regurgitation velocity are recommended for use as indices for identification of diastolic dysfunction.[10] However, no current population-based cohort has yet the power to examine the predictive value of these newest indices, but several including the Tromsø Study have the possibility to validate the older guidelines, but so far this has not been done. Redfield et al[14] validated a tissue Doppler, mitral, and pulmonary vein flow derived definition of diastolic dysfunction against total mortality in a general population, but only tissue Doppler indices are still part of guideline defined diastolic dysfunction. The latest guideline has been validated against left ventricular end-diastolic pressure with a high negative predictive value 93% and area under the curve (AUC) of 0.78,[15] but only the individual components of the 2009 and 2016 guidelines have been validated against mortality and morbidity.[16]

Our aim was to study the long-term risk of all-cause mortality according to diastolic dysfunction measured as LA diameter and the mitral flow Doppler markers such as DT and E/A ratio using a population-based cohort. In addition, we tested the hypothesis that outcome-derived cutoff values of diastolic dysfunction indices are more accurate for predicting fatal outcomes than normal cutoff values derived from a general population.

2 | METHODS

2.1 | Study population

The Tromsø Study was initiated in 1974 as a prospective cohort study with the primary aim of assessing the role of modifiable risk factors for cardiovascular diseases. The study design has been described in detail previously.[17] At present, seven consecutive surveys have been conducted. Both total birth cohorts and random samples from the general population of the Tromsø municipality were invited to participate, and many of the participants attended several surveys. Echocardiography was performed on a random selection of participants in the Tromsø 4 (1994–1995), Tromsø 5 (2001), and Tromsø 6 (2007–2008) surveys.

A total of 3272 participants of the Tromsø 4 survey underwent echocardiographic examination. Of these, 1946 and 1462 had another echocardiographic examination in the Tromsø 5 and/or Tromsø 6 surveys, respectively (Figure 1). The reason that some participants

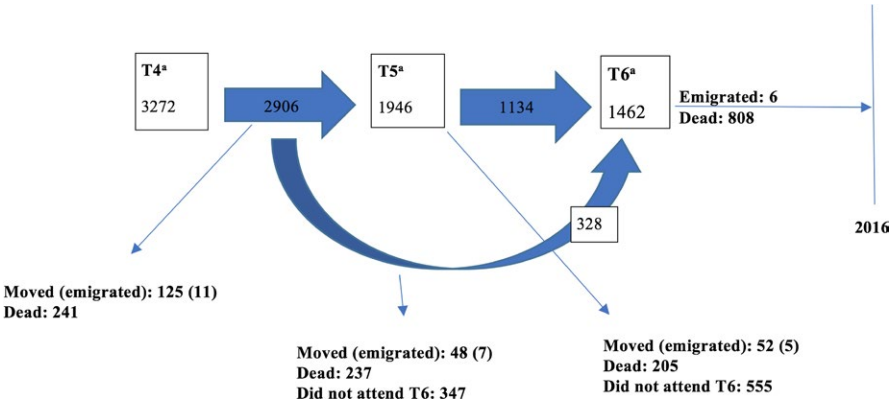

FIGURE 1 Flowchart of the participants with performed echocardiographic examination. The Tromsø Study. [a]Numbers in boxes represent numbers of subjects examined with echocardiography in each wave of the Tromsø Study

at Tromsø 4 did not have further echocardiography examinations at Tromsø 5 and Tromsø 6 is various. They include moving away from the Tromsø municipality (n = 155, out of them n = 21 died afterward), emigration from Norway (n = 18), nonattendance despite being invited (n = 368), and death (n = 457) between Tromsø 4 and Tromsø 6 survey dates.

For the purposes of this analysis, we excluded those aged 50 years or younger (n = 470), those with atrial fibrillation (n = 39) during echocardiographic examination to prevent potential inaccuracy of DT measurements, and those who had LVEF <50% (n = 37) in the Tromsø 4 survey. Following these exclusions, 2734 participants were included in the analyses, each having had echocardiography at Tromsø 4 and possibly at later sweeps. The numbers included in analyses of specific endpoints were slightly smaller due to missing data on these parameters: 2616 participants for LA diameter analysis, 2691 participants for DT analysis, and 2699 participants for E/A ratio analysis. We included 1875 participants from the Tromsø 6 survey in additional analysis of the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′) (E/e′ ratio).

2.2 | Data collection

Information on risk factors and comorbidities was obtained from self-administered questionnaires. Participants provided information on their date of birth, sex, current smoking (yes/no), leisure time physical activity and current use of antihypertensive treatment (yes/no), history of angina (yes/no), myocardial infarction (yes/no), and stroke (yes/no).[17] Body mass index was defined as weight (kg)/height (m^2). Blood pressure was measured using an automated device Dinamap Pro care 300 Monitor (GE Medical Systems Information Technologies, Tampa, FL). Three readings were made after 2 minutes' rest and separated by 1-minute intervals. The mean of the last two readings was used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication. Nonfasting serum levels of total cholesterol and glycated hemoglobin (HbA1c) were measured according to the previously described procedure.[17,18]

2.3 | Echocardiography imaging

The echocardiography in the Tromsø 4 survey was performed by two expert cardiologists using a Vingmed CFM 750 ultrasound scanner (Vingmed Sound A/S, Horten, Norway), and details have been described previously.[7] In the Tromsø 5 and 6 surveys, Acuson Seqoia C258 or C512 scanner (Acuson, Mountain view, CA) was used.[19] Coefficients of variation for intra- and inter-observer variability in the Tromsø 4–6 surveys were less than 10% for chamber dimensions and Doppler-derived values.[19,20]

Echocardiographic assessment was performed with the use of standard imaging planes in the left lateral decubitus position according to ASE and EACVI recommendations.[12] All of the echocardiographic measurements were performed online once per examination, but remeasured online if deviating from eye-balled estimates. M-mode echocardiography was used for LA diameter measurement. LA was measured from the posterior aortic wall to the posterior LA wall using both the parasternal long-axis and short-axis view perpendicular to the aortic root long axis at the level of the aortic sinuses by using the leading edge-to-leading edge convention. LA diameter measurement was performed during end ventricular systole. Body surface area-indexed LA diameter (LA BSA) as 1.5–2.3 cm/m^2 was considered as normal cutoff value range both for men and women. BSA was calculated by the Du Bois formula (BSA = [weight {kg} 0.425 × height {cm} 0.725] × 0.007184).[21]

Doppler examination was performed using the apical 4-chamber view with placing of the 2-mm Doppler sample volume between the mitral leaflet tips. For Doppler measurements, the insonation angle was kept as perpendicular as possible toward the mitral inflow to obtain maximal velocity flow in early diastole. Spectral gain was adjusted until the flow curve became clear relatively to the background.[22] Normal values of DT were considered as 140–220 ms. E/A ratio between 0.8 and 1.5 characterize a normal filling pattern.[10] Values of E/e′ ratio used in analysis were within 4–25.

2.4 | Follow-up and outcome data

Subjects included in the analysis contributed to risk from the date of attendance of the Tromsø 4 survey until date of death, date of emigration from Norway, or the end of follow-up on December 31, 2016, whichever came first. Of the 2734 aged >50 years who had echocardiography at the Tromsø 4 survey, 1399 died during the follow-up period. Table 1 shows the numbers of participants and deaths according to which sweeps they were examined in. In the Cox model, we treated the indices of diastolic dysfunction as time varying covariates. Those participants who had repeat echocardiography examinations in T5 or T6, were still free of atrial fibrillation, and had LVEF≥50%, had their indices of diastolic dysfunction and values for other covariates updated. E/e′ ratio was measured only in the Tromsø 6 survey, giving a follow-up of only 10 years for this parameter.

The all-cause mortality endpoint was identified by linkage of the participants to the National Causes of Death Registry at the Norwegian Institute of Public Health using personal identification number.

TABLE 1 Numbers of participants and deaths included in analyses according to the sweeps of the Tromsø Study in which they had echocardiographic examinations

	Number of participants	Number of deaths
Tromsø 4 only	914	710
Tromsø 4 + Tromsø 5	694	459
Tromsø 5 + Tromsø 6	252	61
Tromsø 4 + Tromsø 5 + Tromsø 6	874	169
Total	2734	1399

Information on the participants who had emigrated from Tromsø was obtained through the Population Register of Norway.

2.5 | Statistical methods

Means with standard deviations and proportions were used to describe baseline characteristics of the study participants according to the three categories of LA diameter (<1.5 cm/m^2; 1.5–2.3 cm/m^2; >2.3 cm/m^2), DT (<140 ms; 140–220 ms; >220 ms), and E/A ratio (<0.8; 0.8–1.5; >1.5). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

Associations of the three echocardiographic variables with all-cause mortality were assessed using time-dependent Cox proportional hazards regression models with fractional polynomials of LA diameter, DT, and E/A ratio as the main predictors. Baseline information for the participants can change during a follow-up period of 23 years. To take into account these changes, we updated baseline information for those participants who also attended following surveys using time-dependent Cox regression. Models were tested for possible interactions between sex and LA diameter, DT, E/A ratio, and E/e′ ratio. We found no interaction between sex and LA diameter, sex and DT, sex and E/A ratio, or sex and E/e′ ratio (P = 0.489, P = 0.696, P = 0.199, and 0.730, respectively), and therefore, results were presented for men and women combined. We chose the best-fitting fractional polynomials of LA diameter, DT, E/A ratio, and E/e′ ratio while adjusting for sex and fractional polynomials of age using the Akaike information criterion.[23] Hazard ratios (HRs) were estimated for a range of LA diameter values from 1.1 to 4.0 cm/m^2, using 1.8 cm/m^2 as the reference value, for a range of DT levels from 80 to 300 ms with 155 ms as the reference value, for a range of E/A ratio levels from 0.3 to 4.0 with 1.1 as the reference value, and for a range of E/e′ ratio from 4 to 25 with 4 as the reference value. HRs with 95% confidence intervals (CIs) were adjusted for sex and fractional polynomials of age because we expected nonlinear associations between age and endpoint. In order to estimate the independent effect of left ventricular filling indices on all-cause mortality, we adjusted the model for systolic blood pressure, total cholesterol, body mass index, smoking, antihypertensive treatment, history of stroke, angina, and myocardial infarction. Likelihood ratio test between a model with and model without fractional polynomial terms of LA diameter, DT, E/A ratio,

TABLE 2 Baseline characteristics of study participants by left atrial diameter (n = 2616); the Tromsø Study 1994–1995

	Left atrial diameter, cm/m^2			
Characteristics	**<1.5 (n = 24)**	**1.5–2.3 (n = 1685)**	**>2.3 (n = 907)**	***P* value**
Death	11 (45.8)	780 (46.3)	524 (57.8)	<0.001
Sex (M-male, F-female)	M-12 (50.0)	M-895 (53.1)	M-392 (43.2)	<0.001
	F-12 (50.0)	F-790 (46.9)	F-515 (56.8)	
Age, y	62.3 (7.1)	62.2 (6.1)	64.7 (6.3)	<0.001
BMI, kg/m^2	25.5 (3.4)	26.2 (3.9)	26.1 (4.0)	0.630
DBP, mm Hg	85.4 (9.6)	84.2 (12.1)	84.5 (13.1)	0.428
SBP, mm Hg	148.7 (21.0)	145.9 (21.4)	149.4 (23.0)	<0.001
Total cholesterol, mmol/L	6.40 (1.12)	6.84 (1.25)	6.81 (1.19)	0.215
HbA1c, %	5.27 (0.36)	5.49 (0.68)	5.49 (0.81)	0.199
History of stroke	1 (3.7)	34 (1.9)	30 (2.5)	0.486
History of angina	2 (7.7)	125 (7.1)	133 (11.8)	<0.001
History of myocardial infarction	0 (0.0)	91 (5.4)	79 (7.6)	0.076
Smoking	9 (36.7)	551 (31.9)	250 (28.6)	0.195
Physical activity				
Low	3 (13.8)	196 (11.9)	122 (12.3)	0.742
Moderate	5 (21.9)	645 (38.1)	336 (38.8)	
Active	13 (59.4)	749 (45.3)	394 (43.5)	
Highly active	1 (4.4)	73 (4.3)	42 (4.9)	
Antihypertensive treatment	4 (16.4)	173 (10.2)	200 (19.7)	<0.001
DT, ms	226.6 (64.5)	204.6 (43.2)	201.1 (46.7)	0.067
E/A ratio	0.85 (0.23)	0.96 (0.27)	1.02 (0.36)	0.086

BMI = body mass index; DBP = diastolic blood pressure; DT = mitral peak E deceleration time; E/A = mitral peak E to peak A ratio; HbA1c = glycated hemoglobin; SBP = systolic blood pressure.
Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

TABLE 3 Baseline characteristics of study participants by deceleration time (n = 2691); the Tromsø Study 1994–1995

Characteristics	Deceleration time, ms			
	<140 (n = 71)	140–220 (n = 1912)	>220 (n = 708)	*P* value
Death	39 (54.9)	863 (45.1)	464 (65.5)	<0.001
Sex (M-male, F-female)	M-27 (38.0) W-44 (62.0)	M-902 (47.2) W-1010 (52.8)	M-404 (57.0) W-304 (43.0)	<0.001
Age, y	62.8 (6.6)	62.4 (6.1)	65.1 (6.2)	<0.001
BMI, kg/m^2	26.7 (3.4)	26.1 (4.0)	26.3 (3.9)	0.307
DBP, mm Hg	86.2 (13.5)	83.7 (12.1)	86.0 (13.1)	<0.001
SBP, mm Hg	151.7 (23.0)	146.8 (21.7)	148.2 (22.9)	<0.001
Total cholesterol, mmol/L	7.00 (1.36)	6.88 (1.23)	6.68 (1.23)	0.006
HbA1c, %	5.52 (0.60)	5.48 (0.69)	5.52 (0.84)	0.073
History of stroke	2 (2.5)	41 (2.0)	26 (2.7)	0.441
History of angina	10 (12.5)	198 (9.6)	65 (6.7)	0.024
History of myocardial infarction	11 (14.8)	117 (6.0)	48 (5.6)	0.010
Smoking	17 (23.5)	588 (30.0)	243 (36.1)	0.006
Physical activity				
Low	13 (18.0)	217 (11.5)	102 (13.3)	0.225
Moderate	28 (39.3)	754 (39.5)	232 (34.7)	
Active	28 (39.5)	834 (44.2)	325 (46.7)	
Highly active	2 (2.8)	85 (4.4)	32 (4.8)	
Antihypertensive treatment	19 (26.5)	254 (13.0)	124 (14.6)	0.006
LA diameter, cm/m^2	2.29 (0.30)	2.21 (0.32)	2.17 (0.33)	0.070
E/A ratio	1.16 (0.49)	1.01 (0.29)	0.87 (0.24)	<0.001

BMI = body mass index; DBP = diastolic blood pressure; E/A = mitral peak E to peak A ratio; HbA1c = glycated hemoglobin; LA = left atrium; SBP = systolic blood pressure.
Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

or E/e′ ratio was used to test the associations. The proportional hazard assumption was met in all models.

The best cutoff values for LA diameter, DT, and E/A ratio were estimated using receiver operating characteristic (ROC) curves and AUCs. We used the maximum value of Youden's index as a criterion for selecting the optimal cutoff points for LA diameter, DT, and E/A ratio.[24] For the two latter with an U-shaped relation to risk, ROC curves were estimated for the upper and lower part of values separately.

A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

2.6 | Ethical considerations

The study conformed to the principles outlined in the Declaration of Helsinki, and the Tromsø Study protocol was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2009/2536/REK North). Informed consent was obtained from all individual participants included in the study.

3 | RESULTS

3.1 | Baseline characteristics

The baseline clinical and echocardiographic characteristics of the study participants are presented according to the three ASE and EACVI categories of LA diameter (Table 2), DT (Table 3), and E/A ratio (Table 4).

3.2 | LA diameter, DT, E/A and E/e′ ratios, and all-cause mortality

We found that models with LA diameter, DT, and E/A ratio adjusted for age and sex showed the very similar pattern of HRs compared to the fully adjusted models. We identified a U-shaped association between LA diameter and all-cause death (Figure 2). When adjusted for sex and age, participants with LA diameter of 1.1 cm/m^2 had a higher risk of death compared with those with LA diameter of 1.8 cm/m^2 (HR = 4.35; 95% CI 1.84–10.30). For values above the reference, significant increase in the risk of death was observed

TABLE 4 Baseline characteristics of study participants by mitral peak E to peak A ratio (n = 2699); the Tromsø Study 1994–1995

	E/A ratio			
Characteristics	**<0.8 (n = 786)**	**0.8–1.5 (n = 1800)**	**>1.5 (n = 113)**	***P* value**
Death	510 (64.9)	811 (45.1)	50 (44.3)	<0.001
Sex (M-male, F-female)	M-367 (46.7)	M-899 (49.9)	M-68 (60.2)	0.021
	W-419 (53.3)	W-901 (50.1)	W-45 (39.8)	
Age, y	65.9 (6.0)	62.1 (6.0)	62 (6.3)	<0.001
BMI, kg/m^2	26.8 (4.1)	25.9 (3.9)	24.9 (3.6)	<0.001
DBP, mm Hg	88.3 (13.3)	82.9 (11.8)	80.2 (11.5)	<0.001
SBP, mm Hg	152.3 (22.9)	145.4 (21.0)	143.1 (21.4)	<0.001
Total cholesterol, mmol/L	6.86 (1.25)	6.83 (1.23)	6.59 (1.13)	0.039
HbA1c, %	5.54 (0.87)	5.47 (0.67)	5.39 (0.50)	<0.001
History of stroke	31 (2.8)	35 (1.9)	3 (3.0)	0.209
History of angina	94 (8.4)	157 (8.3)	19 (19.1)	0.002
History of myocardial infarction	63 (6.3)	94 (5.2)	18 (18.0)	<0.001
Smoking	238 (32.5)	581 (31.3)	31 (25.1)	0.288
Physical activity				
Low	122 (13.9)	208 (11.9)	7 (6.8)	0.242
Moderate	280 (37.9)	687 (38.1)	46 (39.2)	
Active	348 (44.3)	790 (44.7)	53 (47.9)	
Highly active	24 (3.2)	89 (4.9)	6 (5.1)	
Blood pressure treatment	153 (15.9)	228 (12.7)	16 (15.8)	0.077
DT, ms	221.5 (52.1)	197.8 (38.6)	179.3 (35.5)	<0.001
LA diameter, cm/m^2	2.16 (0.32)	2.21 (0.31)	2.36 (0.41)	<0.001

BMI = body mass index; DBP = diastolic blood pressure; DT = mitral peak E deceleration time; E/A = mitral peak E to peak A ratio; HbA1c = glycated hemoglobin; LA = left atrium; SBP = systolic blood pressure.

Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

starting from 2.1 cm/m^2 (HR = 1.09; 95% CI 1.01–1.18). In the fully adjusted model, risk of death was 4.60 and 5.72 times higher for those with LA diameter of 1.1 and 4.0 cm/m^2, respectively when compared to LA diameter of 1.8 cm/m^2.

Left atrial diameter of 1.8 cm/m^2 corresponded to the lowest HR in both age- and sex-adjusted and fully adjusted models (Figure 2), and accordingly, we estimated the optimal cutoff points based on ROC curve analysis above and below this value. The AUC for LA diameter values ≤1.8 cm/m^2 was 0.56 (P = 0.117). The optimal lower cutoff value for LA diameter was estimated as 1.7 cm/m^2. For those with LA diameter >1.8 cm/m^2, the AUC value was 0.60 (P < 0.001) with an optimal upper cutoff point for LA diameter of 2.3 cm/m^2 (Table 5).

Association between mitral peak E DT and risk of all-cause death was U-shaped (Figure 3). In the sex- and age-adjusted model, those with DT of 80 ms had approximately four times higher risk of death compared with the reference value of 155 ms (HR = 4.65; 95% CI 2.37–9.12). Those with DT of 300 ms had a 55% increased risk of death compared with the reference value. In the fully adjusted model, when compared to the reference DT of 155 ms, HRs for DT of 80 ms and DT of 300 ms were 5.37 (95% CI 2.64–10.94) and 1.44 (95% CI 1.23–1.68), respectively. DT less than the reference of 155 ms was associated with increased risk of death starting from DT of 130 ms (HR = 1.09; 95% CI 1.02–1.17) (Figure 3).

The DT value of 155 ms conferred the lowest risk, and the population was accordingly divided at this value. For those with DT levels ≤155 ms (AUC = 0.56, P = 0.030), an optimal cutoff point was 150 ms. AUC for those with DT >155 ms was 0.60, P < 0.001. Here a value of 200 ms was the best cutoff point with 67% sensitivity and 50% specificity (Table 5).

Similarly to LA and DT, the association between mitral valve E/A ratio and risk of death was U-shaped. Sex- and age-adjusted HRs of death for E/A ratio of 0.3 and for E/A ratio of 4.0 compared with E/A ratio of 1.1 were 4.63 and 5.00, respectively. In the fully adjusted model, HRs for E/A ratio of 0.3 and of 4.0 in comparison with the reference value were 4.12 (95% CI 2.66–6.40) and 4.50 (95% CI 2.64–7.67), respectively (Figure 4).

Results of the analysis of E/A ratios and HRs showed that a value of 1.1 had the lowest HR and at this value the population was

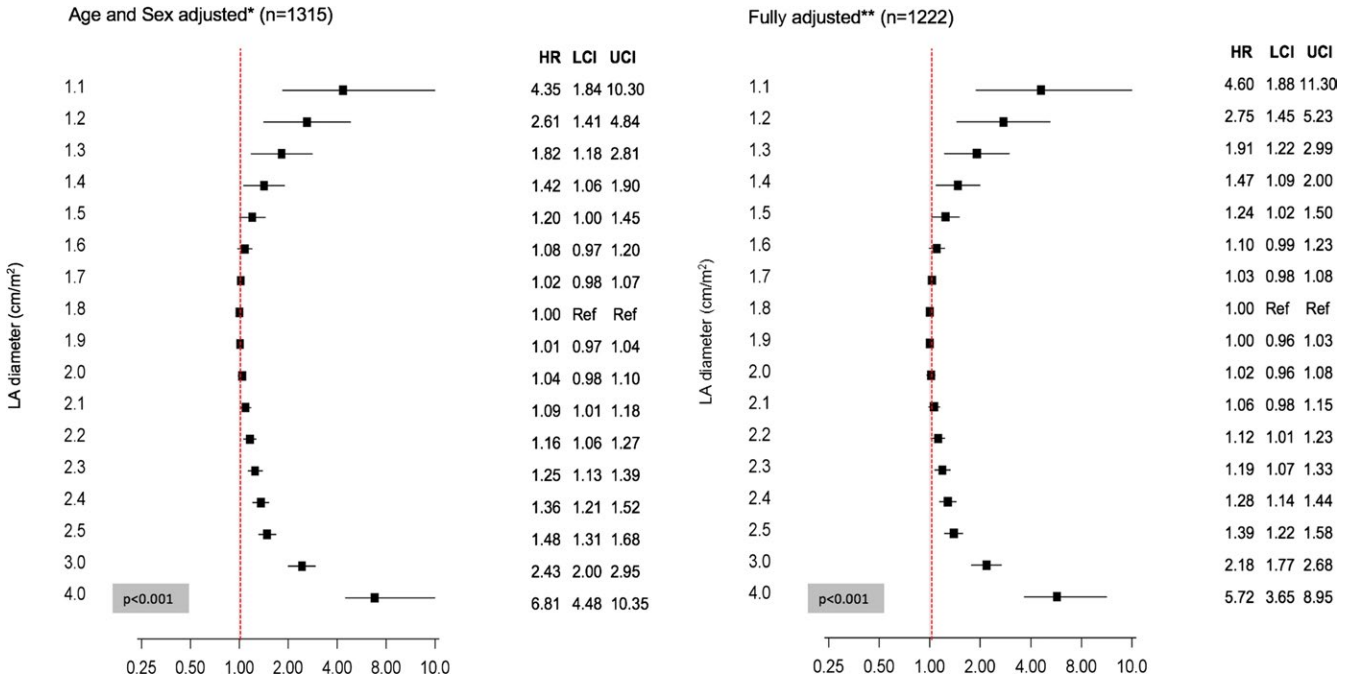

FIGURE 2 Left atrial (LA) diameter and all-cause mortality. The Tromsø Study. *P*-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of LA diameter. *Adjusted for sex and fractional polynomials of age. **Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, and antihypertensive treatment. HR = hazard ratio; LCI = lower 95% confidence interval; UCI = upper 95% confidence interval

TABLE 5 Optimal cutoff values of left ventricular filling indices associated with all-cause mortality outcome; the Tromsø Study

	Optimal cutoff values[a]	Sensitivity/Specificity, %	Youden index	AUC[b] (95% CI)	ROC curve *P*-value	Optimal cutoff values[c]
LA diameter, cm/m^2						
Upper cutoff	2.3	46/71	0.17	0.60 (0.58–0.62)	<0.001	2.1
Lower cutoff	1.7	71/46	0.16	0.56 (0.49–0.63)	0.117	1.4
DT, ms						
Upper cutoff	200	67/50	0.17	0.60 (0.58–0.63)	<0.001	185
Lower cutoff	150	98/18	0.16	0.56 (0.51–0.62)	0.030	120
E/A ratio						
Upper cutoff	1.2	67/46	0.14	0.58 (0.53–0.63)	<0.001	1.4
Lower cutoff	0.6	17/89	0.06	0.54 (0.52–0.57)	<0.001	0.8

AUC = area under the curve; DT = mitral peak E deceleration time; E/A = mitral peak E to peak A ratio; LA = left atrium; ROC = receiver operating characteristic.

[a]Optimal cutoff values for all-cause mortality outcome estimated according to the highest Youden index.

[b]AUCs for ranges which include optimal (maximal Youden index based) upper and lower cutoff values. Ranges are estimated above and below the values with lowest HRs for LA diameter: 1.8 cm/m^2; for DT: 155 ms; for E/A ratio: 1.1

[c]Optimal cutoff values for all-cause mortality outcome derived from time-dependent Cox regression models adjusted for age and sex.

divided into two groups. Lower part of values with E/A ratio ≤1.1 had an AUC of 0.54, $P < 0.001$. An optimal cutoff was considered as 0.6. Results of ROC curve analysis for those with E/A ratio >1.1 showed that AUC was 0.58, $P < 0.001$. The best cutoff value for E/A ratio >1.1 equals 1.2 with levels of sensitivity of 67% and specificity of 46% (Table 5).

Optimal cutoff values for all-cause mortality derived from time-dependent Cox regression models adjusted for age and sex were 1.4–2.1 cm/m^2 for LA diameter, 120–185 ms for DT, and 0.8–1.4 for E/A ratio (Table 5).

Comparison between ROC curves and AUCs of models with new outcome-derived, maximal Youden index-based reference values with different variables showed that the largest AUC of 0.63 was estimated when LA diameter cutoff was combined with similarly derived cutoffs for DT and E/A ratio. Combination of LA diameter with DT gave similar AUC. Other combinations of LA diameter with

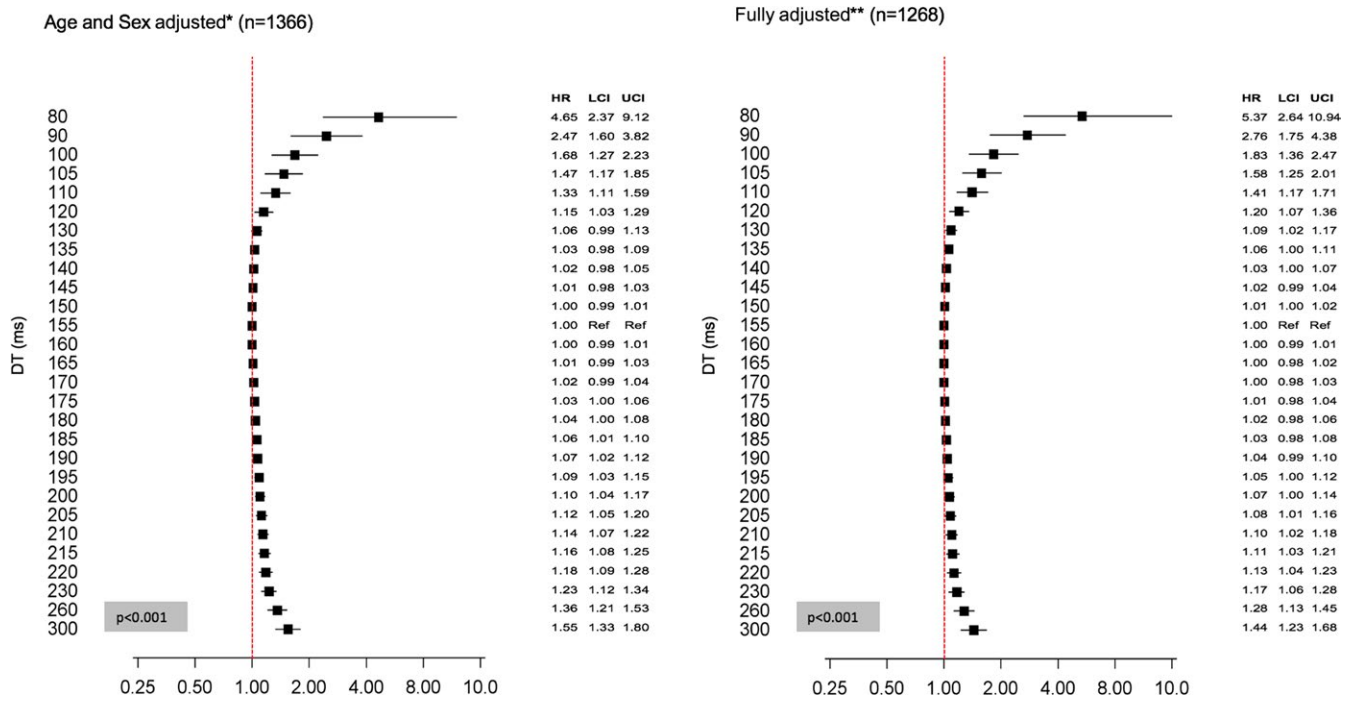

FIGURE 3 Mitral peak E deceleration time (DT) and all-cause mortality. The Tromsø Study. *P*-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of DT. *Adjusted for sex and fractional polynomials of age. **Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, and antihypertensive treatment. HR = hazard ratio; LCI = lower 95% confidence interval; UCI = upper 95% confidence interval

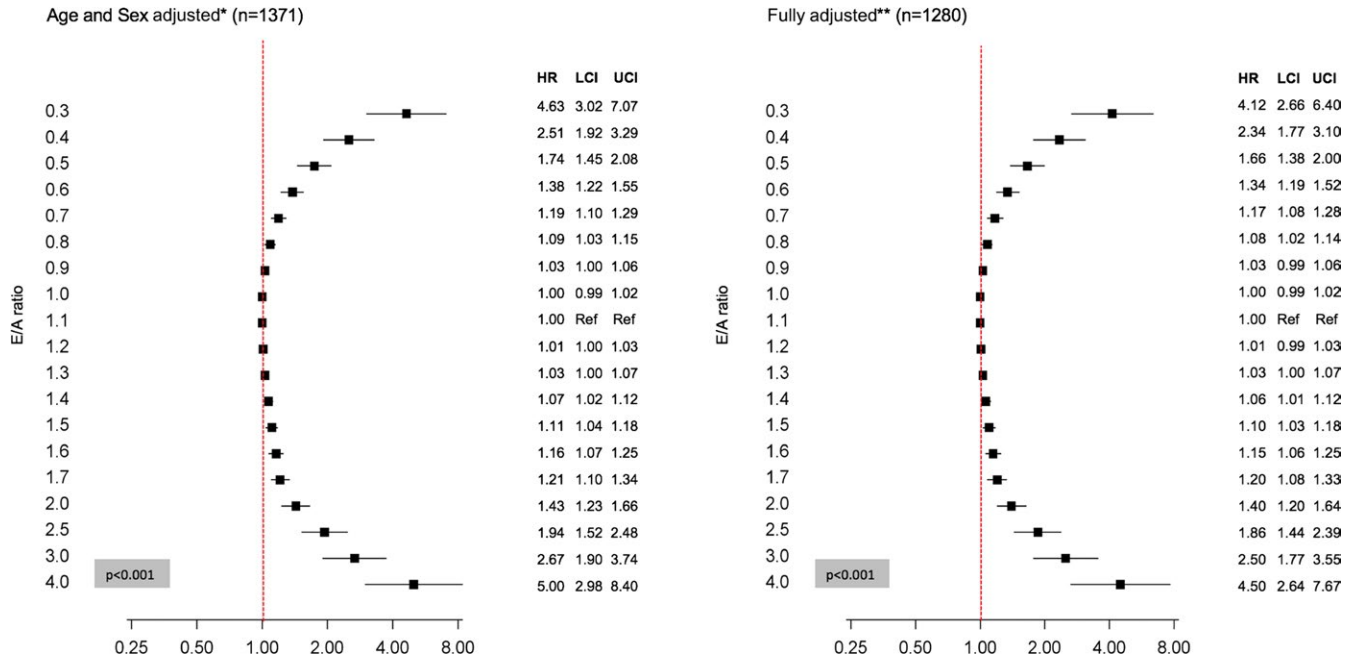

FIGURE 4 Mitral peak E to peak A ratio and all-cause mortality. The Tromsø Study. *P*-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/A ratio. *Adjusted for sex and fractional polynomials of age. **Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, and antihypertensive treatment. HR = hazard ratio; LCI = lower 95% confidence interval; UCI = upper 95% confidence interval

left ventricular filling indices did not result in increase of AUC. HR-derived cutoffs produced identical AUCs and were not presented.

Receiver operating characteristic analysis using ASE and EACVI recommended cutoffs revealed the highest AUCs when LA diameter was combined with DT and with DT+E/A ratio. These combinations gave AUCs of 0.63.

We revealed a cubic association between E/e′ ratio and all-cause mortality (Figure 5). In the age- and sex-adjusted model, those with

E/e′ of 25 had 3.48-fold increase of overall mortality risk in comparison with reference value of 4. In the fully adjusted model, the risk of all-cause mortality in those with the extreme E/e′ value compared with E/e′ of 4 was 4.54 (95% CI 1.80–11.44).

The AUC's for models with E/e′ ratio, LA diameter, DT, or E/A ratio as predictors of all-cause mortality from 2007 and onwards were 0.59 (95% CI 0.54–0.63), 0.60 (95% CI 0.55–0.64), 0.62 (95% CI 0.58–0.66), 0.60 (95% CI 0.56–0.64), respectively. No significant difference was found between the models with echocardiographic determinants of diastolic dysfunction and all-cause mortality.

4 | DISCUSSION

4.1 | Results overview

Our study reveals that echocardiographic markers of diastolic dysfunction such as LA diameter, DT, and E/A ratio can be used for prediction of all-cause mortality risk. We were able to estimate HRs for all of the described parameters, assess new outcome-derived cutoff points for them, and describe the best combinations of echocardiographic markers for all-cause mortality outcome prediction. The association remained U-shaped after additional adjustment for systolic blood pressure, body mass index, total cholesterol, smoking, antihypertensive treatment, history of stroke, angina, and myocardial infarction. It shows that LA diameter, DT, and E/A ratio each has independent effects on all-cause mortality also after adjustment for sex, age, and cardiovascular risk factors. We also used all-cause mortality risk estimation models for assessing optimal cutoffs of the left ventricular filling indices. These cutoffs were slightly different from those obtained with maximal Youden index but gave identical prediction ability for all-cause mortality outcome.

4.2 | Comparison with other studies

4.2.1 | Left atrial diameter

Left atrial diameter has been shown to be an important prognostic parameter of mortality in several but not all studies conducted in general population samples.[5,25] Pritchett et al[26] reported that BSA-indexed LA volume was not associated with all-cause mortality when adjusted for age, gender, ejection fraction, and diastolic dysfunction grade. Diversity in results may be explained by differences in the study populations, methods of LA diameter measurement, and indexation.

In our study, the HRs for LA diameter above the reference of 1.8 cm/m^2 increased from 1.12 (1.01–1.23) to 5.72 (3.65–8.95) in the fully adjusted model corresponding to previous publications.[25] The underlying mechanisms linking an enlarged LA diameter with increased all-cause mortality have been described previously.[27] Elevated LA filling pressures, decreased flow velocities in LA appendages, atrial fibrillation as well as structural heart disease and hypertension are among those mechanisms which result in all-cause mortality risk increase.

A novel finding of our study is that LA diameter below 1.5 cm/m^2 independently increases risk of all-cause death. This finding is supported by a few recent studies, however with several limitations. Aviram et al[28] found that decreased LA volume was associated with increased mortality risk in patients with acute pulmonary embolism. Rozenbaum et al[29] also reported that patients with very small LA

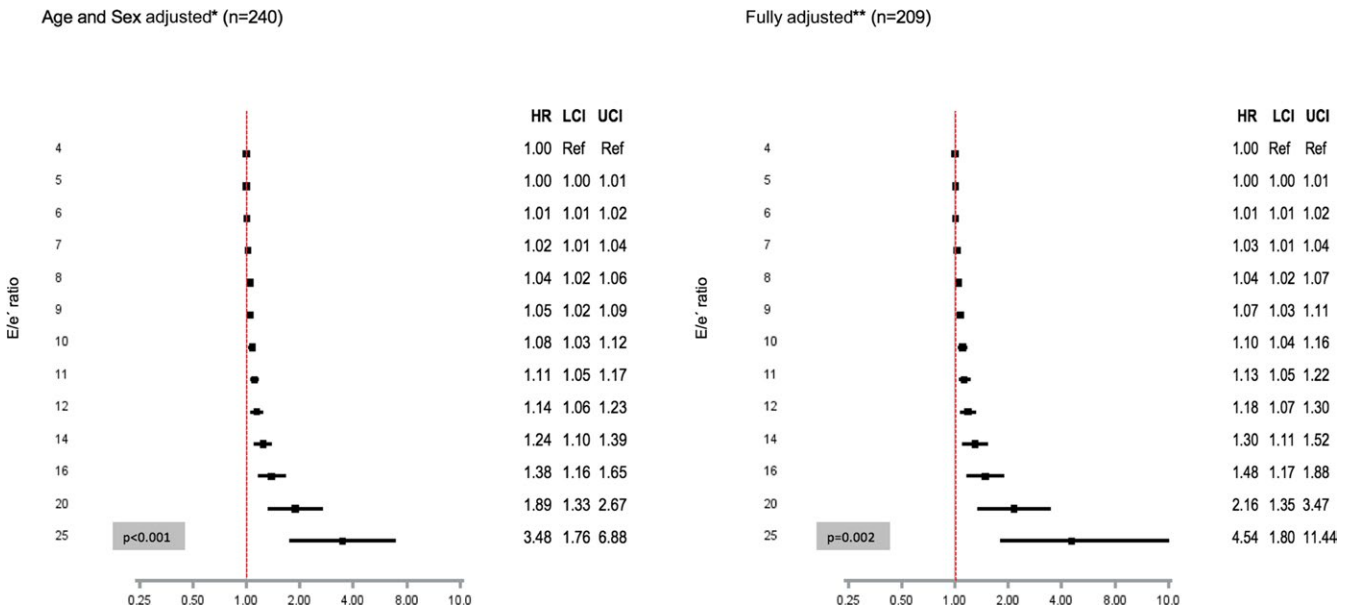

FIGURE 5 Mitral peak E to peak e′ ratio and all-cause mortality. The Tromsø Study. *P*-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/e′ ratio. *Adjusted for sex and fractional polynomials of age. **Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, and antihypertensive treatment. HR = hazard ratio; LCI = lower 95% confidence interval; UCI = upper 95% confidence interval

volume index <24 mL/m^2 had HR of 3.6 (95% CI: 1.46–8.87) for all-cause mortality. Limitations of these studies were small sample sizes and short follow-up periods. Acquisition of images in these studies was based on computed tomography. To our knowledge, there are no literature data on the association of small atrial diameters and all-cause mortality rates based on two-dimensional echocardiography.

One of the possible explanations of association between small LA size and mortality could be a decrease of LA emptying fraction, a functional parameter, which is independently associated with LA remodeling and mortality prediction.[30]

According to our findings, 11 individuals with LA diameter <1.5 cm/m^2 died during the follow-up. Cause of death of two individuals was not established. Only one person had myocardial infarction as cause of death indicating a maximal possible proportion of cardiovascular death to 30%. In patients with LA diameter >2.3 cm/m^2, most of the mortality were due to myocardial infarction 191 (40.1%) and ischemic heart disease 78 (16.4%). Other causes of death in this group were stroke 48 (10.1%), sudden death 10 (2.1%), and subarachnoid hemorrhage 1 (0.2%) indicating less than half the risk of cardiovascular disease death for small atria compared to enlarged.

We defined lower and upper cutoffs with optimal sensitivity and specificity levels using the Youden index. Thus, lower reference cutoff value for LA diameter was 1.7 cm/m^2 (ROC curve *P*-value = 0.117) which is higher than the ASE and EACVI recommended value of 1.5 cm/m^2. According to our findings, the value of 1.5 cm/m^2 has a higher sensitivity level of 81% which corresponds to the higher negative predictive value. The upper cutoff point was 2.3 cm/m^2 with a 46% sensitivity and 71% specificity and had significantly higher risk than 2.1 cm/m^2, which conforms to recent recommendations.[12]

4.2.2 | Mitral peak E deceleration time

In our study, the optimal cutoff level for lower DT reference value was defined as 150 ms which is higher than the current normality-based cutoff of 140 ms.[10] It was a key parameter in Redfield definition[14] and has shown strong independent predictive ability in patient population with myocardial infarction.[31] Our results demonstrate that risk of all-cause mortality increased gradually with decreasing DT starting from 130 ms when compared with the reference value of 155 ms in the fully adjusted model. Our findings can be explained by the inverse relation of DT to the left ventricle filling pressure and association of a short DT with restrictive filling pattern, which increases the risk of left ventricular dilatation.

We found an optimal upper cutoff value of 200 ms with 67% sensitivity and 50% specificity for identification of a fatal outcome. Prolonged DT is associated with low left ventricular filling pressures and impaired ventricular relaxation, which lead to progression of diastolic dysfunction and heart failure. Although the prognostic value of elevated DT has been documented before,[32] this is the first estimation of the diagnostic accuracy of different DT values for prediction of all-cause mortality in a general population.

Unlike the U-shaped relationships between all-cause mortality and LA size or E/A ratio with a narrow normal range, DT effect is linked to extreme values at each end of a wide normal range in concordance with ASE and EACVI normality cutoffs. However, our approach of using outcome-derived values allowed narrowing the fraction of DT middle values and improves risk assessment nonsignificantly.

4.2.3 | E/A ratio

Results from the second wave in the Strong Heart Study indicated that in middle-aged and elderly participants, an E/A ratio level above 1.5 was independently associated with a twofold increase in all-cause mortality risk.[33] E/A levels below 0.6 were similarly associated with increased mortality risk. In our study, the risk of all-cause mortality increased gradually for E/A values above 1.3. Risk of all-cause mortality increased also with decreasing E/A ratios starting from 0.8.

Analysis of the predictive ability of E/A ratio showed that optimal cutoffs differed from those recommended by ASE and EACVI. Thus, the lower optimal cutoff was found as 0.6 with a corresponding 17% sensitivity and 89% specificity. Upper cutoff value of 1.2 had a specificity level of 46% which is lower than ASE and EACVI guideline-based E/A ratio value of 1.5 (specificity 59%) with all-cause mortality as outcome.

4.2.4 | E/e′ ratio

Our findings suggest that an elevated E/e′ ratio is independently associated with increased risk of all-cause mortality in a general population. This is in contrast to Mogelvang et al[34] in the Copenhagen City Heart Study who found no association of E/e′ with overall mortality. Kuznetsova et al[16] reported borderline association of E/e′ ratio and risk of cardiac events. These studies had 90 and 59 cases respectively and half the follow-up time of our study where 240 cases and 10 years follow-up increases power in support of our finding. Interestingly, E/e′ did not have a superior predictive ability for overall mortality when compared with other diastolic dysfunction markers.

4.3 | Comparison of prognostic values of LA diameter, DT, and E/A

We aimed to explore the hypothesis that reference values based on outcome data would predict all-cause mortality better than those recommended by ASE and EACVI. The outcome-derived model, which combines LA diameter, DT, and E/A ratio, showed the best prediction on all-cause mortality, but not significantly different from the model with only LA diameter and DT included.

Using the cutoff values from current ASE and EACVI classification of diastolic dysfunction gave the same AUCs for LA diameter as Youden index-based outcome-derived cutoffs. For models with the three variables combined, the largest AUC was detected in LA

diameter+DT+E/A ratio model (AUC = 0.63, $P < 0.001$) which was the same as in a model with ASE and EACVI cutoff values. When assessing the incremental value of each parameter, both DT and E/A ratio added prognostic value to LA diameter, but E/A ratio did not add to the prognostic accuracy of LA diameter in combination with DT.

4.4 | Study strengths and limitations

This was a large prospective population-based study with a long follow-up period. The prospective design of the Tromsø study and a random sample of a large age span from the general population with a high attendance rate increases generalizability to other Caucasian populations. Another strength was the updating of baseline values as the participants attended following surveys. Although biplane or 3D echocardiography is now regarded as the most accurate methods of LA volume estimation, M-mode anteroposterior LA diameter has higher intra- and inter-observer reproducibility especially while assessing minimal atrial dimensions.[35]

A main limitation of the study is that we used M-mode-based linear measurements of LA which is less accurate than those based on LA volumes performed by biplane method. Unfortunately, LA echocardiographic data from the Tromsø 4–6 surveys contain only M-mode measurements. Our findings need validation using LA volumes which will be explored in future studies. The raw images from Tromsø 4–6 surveys are available as well as measurements of volumes from the latest Tromsø 7 survey (2015–2016), which when enough endpoints have occurred, will give us the possibility to perform further analysis of LA volumes and diastolic dysfunction patterns according to the recent recommendations. Tricuspid regurgitation was not measured in the Tromsø 4–6 surveys. E/A ratio pseudonormal filling pattern was not considered in our study. However, individuals with severe left ventricular dysfunction were excluded from the study, and we suppose that influence of pseudonormalization was relatively small. Information on smoking, current use of antihypertensive treatment, and history of angina, myocardial infarction, and stroke was self-reported. It could potentially result in the presence of information bias. Models were not adjusted for laboratory markers such as N-terminal pro-brain natriuretic peptide due to inconsistent presence of these parameters in all studied waves of the Tromsø Study. The maximal Youden index as classic data-driven approach for optimal cutoff estimation has its own disadvantages. The main is that Youden index is not sensitive for differences in the sensitivity and specificity of the test. To avoid the limitation, we presented optimal cutoff points based on HRs along with cutoff values based on maximal Youdex index. The study only assesses the ability to predict mortality. As presence of diastolic dysfunction is associated with an increased risk of developing heart failure as well as death, estimation of cutoff values based on a composite endpoint of death and heart failure could have yielded different results and potentially a higher predictive accuracy.

5 | CONCLUSIONS

Our study concludes that not only enlarged but also small LA diameter is associated with increased all-cause mortality risk. Using our new outcome-derived cutoffs of LA diameter, DT, and E/A ratio did not result in a better predictive ability for all-cause mortality in comparison with current ASE and EACVI recommended cutoff points. A combination of the Doppler-based LV filling parameter DT with LA diameter is preferable while assessing risk of all-cause mortality, while E/A ratio did not add incremental value.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Paper II
+ Supplement

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ORIGINAL PAPER

Global myocardial longitudinal strain in a general population—associations with blood pressure and subclinical heart failure: The Tromsø Study

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Abstract

The early detection of subclinical myocardial dysfunction can contribute to the treatment and prevention of heart failure (HF). The aim of the study was to (i) describe myocardial global longitudinal strain (GLS) patterns in a large general population sample from Norway and their relation to established cardiovascular disease (CVD) risk factors; (ii) to determine its normal thresholds in healthy individuals and (iii) ascertain the relation of myocardial GLS to stage A subclinical heart failure (SAHF). Participants (n = 1855) of the 7th survey of the population-based Tromsø Study of Norway (2015–2016) with GLS measurements were studied. Linear and logistic regression models were used for assessment of the associations between CVD risk factors and GLS. Mean GLS (SD) in healthy participants was − 15.9 (2.7) % in men and − 17.8 (3.1) % in women. Among healthy subjects, defined as those without known cardiovascular diseases and comorbidities, GLS declined with age. An increase of systolic blood pressure (SBP) of 10 mm Hg was associated with a 0.2% GLS reduction. Myocardial GLS in individuals with SAHF was 1.2% lower than in participants without SAHF ($p < 0.001$). Mean myocardial GLS declines with age in both sexes, both in a general population and in the healthy subsample. SBP increase associated with GLS decline in women. Our findings indicate high sensitivity of GLS for early subclinical stages of HF.

Keywords Global longitudinal strain · Heart failure · Systole · Arterial hypertension · Echocardiography · Epidemiology

Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide [1]. Global myocardial longitudinal strain (GLS) is a derived deformation parameter, enabling detection of subtle left ventricular (LV) function abnormalities. GLS is superior to LV ejection fraction (LVEF) in prediction of cardiovascular mortality in patients with chronic kidney disease [2], all-cause mortality in patients with systolic heart failure (HF) [3] and atrial fibrillation [4]. Furthermore, myocardial GLS was found to be an independent predictor of the adverse outcomes after acute myocardial infarction (MI) [5], infective endocarditis [6], aortic stenosis [7], hypertrophic cardiomyopathy [8] and stroke [9]. The role of myocardial GLS in CVD mortality prediction in populations with low CVD risk has also been investigated [10]. In patients with arterial hypertension, myocardial GLS was related to structural remodeling of the LV [11]. Kuznetsova et al. have recently shown that high mean arterial pressure was associated with a decline in GLS over a follow-up of 4.7 years [12]. However, there are few studies of the associations between systolic

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blood pressure (SBP), hypertension treatment and GLS in general unselected populations.

To date there is no consensus, and thus no established clinical guidelines [13, 14], as to what constitutes cut points for normal myocardial GLS, however peak GLS level of − 20% mentioned as expected in healthy persons [13]. Assessment of cut off points of normal myocardial GLS in healthy individuals have produced varying results. Most population studies find higher reference values in healthy subjects [15, 16].

Stage A subclinical HF (SAHF) define individuals with absence of clinical symptoms or structural heart disease but presence of risk factors for HF [17]. SAHF progression is associated with impairment of structural and functional state of the heart over time with progression to the next stage of HF [18]. Myocardial GLS has improved prediction of subsequent clinical HF in patients with Stage B subclinical HF [19] and myocardial GLS is already known to be related to SAHF in high risk groups [20–22]. However, whether this applies to the whole SAHF group is, to the best of our knowledge, unknown. Whether GLS adds information in SAHF group beyond CVD risk factors and self-reported dyspnea symptoms in a general population has yet to be elucidated.

The main aim of our study is to describe peak-myocardial GLS in a large general population sample from Norway and their relation to established CVD risk factors. Secondary aims are to determine GLS normal thresholds in healthy individuals and the relation of myocardial GLS to SAHF.

Methods

Study population

The Tromsø Study is a prospective cohort study, which was initiated in 1974 with the aim of assessing the role of known modifiable risk factors for CVD in Northern Norway and detection of new targets for prevention of CVD. The design of the study was described in previous publications [23]. Seven consecutive surveys have been conducted. Our study sample included 840 men and 1015 women from 7th survey in The Tromsø Study who underwent echocardiography and had myocardial GLS data (Fig. 1). We excluded those with missing values on risk factors (n = 108) leaving 1747 individuals aged 40–99 years for the main analyses.

Data collection

Self-reported history of MI, HF, atrial fibrillation, angina, stroke, diabetes, chronic obstructive pulmonary disease was collected by questionnaires. Additionally, we included those who experienced atrial fibrillation during echocardiography as atrial fibrillation "positive" individuals. Participants with HbA1c ≥ 6.5% were treated as having diabetes regardless of self-reported status. Breathlessness was assessed by the modified UK Medical Research Council (mMRC) breathlessness/dyspnea scale [24].

Blood pressure (BP) was measured three times with 1-min intervals using an automated device Dinamap Pro care 300 Monitor (GE Medical Systems Information Technologies, Tampa, FL, USA). The mean of the last two readings was used in the analysis. Hypertension was defined as SBP ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg or self-reported use of antihypertensive medication. Metabolic syndrome was defined according to American Heart Association (AHA)/National Heart, Lung and Blood Institute statement [25].

Study groups definitions

Healthy persons were defined as those without known cardiovascular diseases and comorbidities. We excluded those with hypertension, diabetes, atrial fibrillation, HF, angina, MI, stroke, chronic obstructive pulmonary disease and ejection fraction of the left ventricle (LV EF) < 50% leaving a "healthy" subsample of 1068 individuals (Fig. 1). To assess the effect of increasing echocardiographic pathology by age we additionally excluded from the healthy subsample those with severe valve dysfunction, LV or left atrial (LA) enlargement or severe tricuspid regurgitation (> 2.8 m/s).

For defining the SAHF individuals we excluded subjects (n = 1146) with known CVD (previous history of MI, HF or stroke) and echocardiographic geometric LV abnormalities (Left ventricular myocardial mass index (LVMMi) > 50 in men and > 47 in women; relative LV wall thickness (rwt) > 0.42 or rwt ≤ 0.42 with LVMMi > 50 in men and > 47 in women), LV EF < 50%, and severe valve dysfunction (mitral and aortic stenosis and regurgitation ≥ grade 3) (Fig. 1). Thus, we identified a subset of 709 individuals who may include those with SAHF. In the American College of Cardiology Foundation/AHA guidelines guidelines [17], SAHF is defined as the presence of at least one of the following conditions: diabetes, metabolic syndrome, obesity, arterial hypertension or angina. Applying these criteria, we identified 220 individuals with SAHF (Fig. 1).

Echocardiography imaging

In The Tromsø 7 Study echocardiography was performed by a qualified sonographer using a GE Vivid E9 (GE Medical, Horten, Norway) ultrasound scanner. Offline image reading using EchoPac software (EchoPac version 113; GE Medical, Horten, Norway) was performed by one reader (MS).

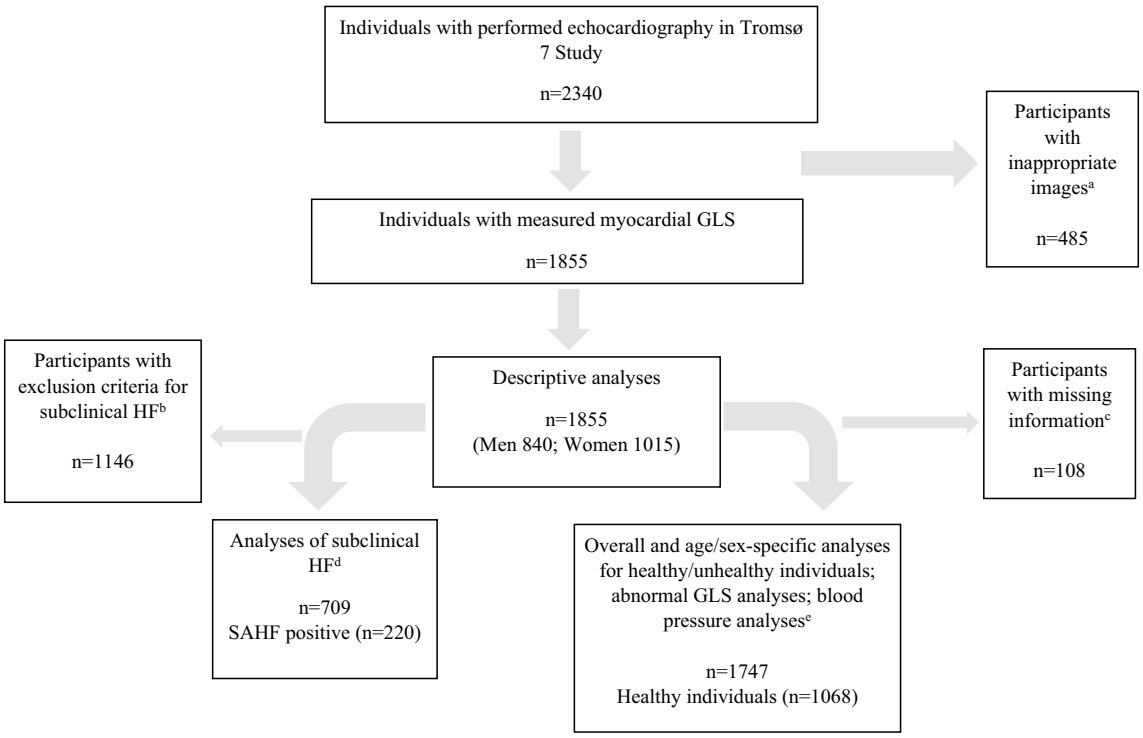

Fig. 1 Flowchart of the study participants. The Tromsø Study (2015–2016). [a]Participants excluded from GLS analysis due to inappropriate imaging quality. [b]Individuals with any of the following: left ventricle geometry abnormalities, left ventricle ejection fraction < 50%, severe valvular heart disease, history of myocardial infarction, heart failure or stroke. [c]Missing information on any of the following variables: myocardial infarction, angina, stroke, bronchitis, hypertension, diabetes, atrial fibrillation, heart failure, HbA1c, left ventricle ejection fraction. [d]Included those with the present at least one of the following: diabetes, metabolic syndrome, obesity, arterial hypertension, angina. [e]Five individuals with missing information were excluded from GLS analyses according to SBP groups. One individual excluded from logistic regression analysis

Conventional echocardiography

Cineloops were recorded using standard 4-chamber, 2-chamber and long-axis apical views according to a prespecified protocol [26]. We obtained the images at a framerate of 50–70 frames per second. Ultrasound examinations were performed according to American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines [13] in the left lateral decubitus position. M-Mode images were aligned in the parasternal long axis view and recorded in the short axis view. LV myocardial mass was calculated according to ASE guidelines and indexed by height$^{2.7}$ [13]. LVEF and LA volume were calculated using the biplane Simpson's method. LA volume was indexed (LAVi) by body surface area (BSA) [27]. Mitral valve Doppler measurements were performed with a Doppler sample volume of 2-mm placed between the tip of the mitral leaflets in the apical 4-chamber view. We adjusted the spectral gain until the flow curves became clear [28]. The insonation angle for Doppler measurements was kept perpendicular toward the mitral inflow. Maximal velocity flow was measured in early diastole and after atrial p-wave.

Tissue Doppler parameters such as peak septal and lateral é were derived from apical 4-chamber view with 5-mm sample volume located at the septal and lateral side of the mitral annulus. Abnormal echo parameters considered as tricuspid regurgitation velocity > 2.8 m/s; LAVi > 34 ml/m^2 [29].

Two-dimensional strain

Two-dimensional strain was analyzed according to EACVI/ASE common standards for 2D speckle tracking echocardiography [30]. The endo- and epicardial borders were initially traced with the use of automated function imaging. Myocardial GLS values were obtained from averaging of endo- mid- and epicardial layer's GLS values from three apical views based on 17-segment model. Images were checked visually for clear visibility of the endo- and epicardial borders during the entire cardiac cycle. Attention was paid to accurate placement of region of interest (ROI) with the aim

of avoiding inclusion of extracardiac structures. Furthermore, we paid attention not to include papillary muscles in contour of LV or the fibrous part of the basal inferoseptum or LV outflow tract [31]. ROI was visually assessed and manually adjusted in case of inappropriate tracking. Views with more than two segments with inappropriate tracking were excluded from the analysis.

Statistical methods

The study population included individuals aged from 40 to 99 years divided in 10-year age groups. Baseline characteristics of the study participants were described with the use of means with standard deviations and proportions. For analyses of associations between myocardial GLS and SBP we divided study population by the following SBP groups: < 120, 120–129, 130–139, 140–159, 160–169, 170–179 and ≥ 180 mm Hg.

According to the sex-specific SBP groups, means for myocardial GLS were adjusted for age using linear regression analysis. Absolute means were tabulated for those aged 63 years. Comparisons between groups were performed by analysis of variance (ANOVA), χ^2 test and Fisher's exact test. For analysis of GLS change by age we used weighted linear regression. The "Weight" variable for regression equation was estimated from number of individuals in each age group. Lower limit of normal (LLN) myocardial GLS for "healthy" subpopulation was defined as absolute mean GLS minus 1.96*standard deviation. Bootstrapping with 1000 samples was used to define upper 97.5th and lower 2.5th percentiles for LLN with confidence intervals [32]. We used quantile regression for estimation of the *p* value for trend of LLN change by age. Logistic regression models were applied to estimate odds ratios (OR) for different risk factors of myocardial GLS below age and sex-specific LLN (abnormal GLS). The OR for each of the following predictors (BMI, history of: MI, atrial fibrillation, angina, diabetes, stroke, arterial hypertension and breathlessness scale) were estimated separately.

Intra- and inter-reader variability of myocardial GLS was assessed in recordings of 27 of 30 randomly selected participants. Three individuals were excluded due to inappropriate image quality. Intra-reader variability was assessed in repeated GLS measurements by one reader (M.S) with 3-months intervals. To assure external validity of measurements as well as internal inter-reader variability was assessed with two readers (M.S. and A.R and presented as intra-class correlation coefficients (ICC) and mean difference ± SD. Coefficient of repeatability (CR) was calculated using the formula 2.77*SD_w with SD_w as the within-subject standard deviation. Visual assessment of inter-observer variability was performed with use of a Bland–Altman plot.

A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Descriptive characteristics

The descriptive echocardiographic and clinical characteristics of the study population are presented in 10-year age groups (Table 1). Study sample included 840 (45.3%) men and 1015 (54.7%) women. The prevalence of self-reported pathology increased across the entire age range except for MI, diabetes and angina pectoris which have the highest prevalence in 70–79 years individuals. Of the echocardiographic characteristics: LVMMi, LAVi, Mitral E-wave deceleration time (DT), E/e′ ratio showed a linear relation to age, while LVEF and E/A ratio did not.

Myocardial GLS in The Tromsø 7 Study

In our general population sample, mean myocardial GLS declined with age in both men and women (Fig. 2).

Myocardial GLS of the healthy participants

The prevalence of healthy individuals by age from The Tromsø 7 Study sample according to the healthy/unhealthy criteria is presented in Table 2. We found that the prevalence of healthy women was stable between 40 and 59 with a decline after 60 years of age (p for change of healthy proportions by age < 0.001). In men the decrease of healthy individuals starts earlier than in women but then follows the same slope by age ($p < 0.001$). There was no interaction between age group and sex ($p = 0.457$).

Mean myocardial GLS (SD) in healthy participants ($n = 1068$) was − 15.9 (2.7) % in men ($n = 451$) and − 17.8 (3.1) % in women ($n = 617$). Figure 2 describes mean levels of myocardial GLS in healthy participants according to age and sex. Healthy women had higher values of myocardial GLS than men in all age groups. Significant change of mean myocardial GLS by age was observed for both sexes ($p = 0.001$ and < 0.001 in men and women respectively). In the healthy subgroup without echo abnormalities the age effect on GLS was no longer significant in men (p-value for men 0.179, for women < 0.001).

The comparison of GLS in healthy versus unhealthy individuals is demonstrated in Online Resources 2 (for men) and 3 (for women) as well as the numbers of individuals with measured myocardial GLS (Online Resource 4).

Table 1 Descriptive characteristics of the participants who underwent echocardiography and had their myocardial GLS measured

Characteristics	Total	Age-group (years)				
		40–49	50–59	60–69	70–79	80 +
n (%)	1855 (100)	247 (13.3)	338 (18.2)	694 (37.4)	467 (25.2)	109 (5.9)
BMI, kg/m^2 (SD)	26.9 (4.1)	27.1 (5.0)	26.6 (4.1)	26.8 (3.8)	27.3 (4.2)	26.0 (3.5)
SBP, mm Hg (SD)	133.8 (20.5)	121.2 (15.6)	126.9 (18.2)	133.9 (19.3)	141.3 (19.8)	150.9 (22.0)
DBP, mm Hg (SD)	75.2 (9.9)	74.0 (9.9)	76.1 (9.6)	76.1 (9.8)	74.3 (10.0)	73.5 (9.8)
Antihypertensive treatment, n (%)	612 (33.4)	24 (9.8)	51 (15.2)	229 (33.4)	248 (54.0)	60 (58.3)
Hypertension, n (%)	549 (29.7)	24 (9.8)	45 (13.3)	209 (30.2)	212 (45.5)	59 (54.1)
mMRC scale Grade 0–1, n (%)	1778 (95.9)	239 (96.8)	333 (98.5)	673 (97.0)	436 (93.4)	97 (89.0)
Grade ≥ 2, n (%)	77 (4.2)	8 (3.2)	5 (1.5)	21 (3.0)	31 (6.6)	12 (11.0)
History of MI, n (%)	106 (5.9)	2 (0.8)	2 (0.6)	35 (5.2)	60 (13.4)	7 (7.5)
History of HF, n (%)	67 (3.6)	2 (0.8)	4 (1.2)	20 (2.9)	27 (5.8)	14 (13.2)
History of Stroke, n (%)	59 (3.3)	2 (0.8)	4 (1.2)	22 (3.3)	22 (5.0)	9 (9.2)
History of Angina, n (%)	74 (4.1)	4 (1.6)	1 (0.3)	23 (3.4)	39 (8.8)	7 (7.5)
History of Afib, n (%)	127 (6.9)	9 (3.6)	14 (4.1)	47 (6.8)	45 (9.6)	12 (11.0)
History of diabetes, n (%)	114 (6.2)	9 (3.6)	7 (2.1)	43 (6.2)	51 (10.9)	4 (3.7)
History of bronchitis, n (%)	16 (0.9)	2 (0.8)	3 (0.9)	4 (0.6)	3 (0.7)	4 (4.2)
LVMMi, g/m$^{2.7}$, n (SD)	43.9 (14.1)	38.4 (10.8)	40.2 (11.3)	44.4 (13.3)	47.7 (15.9)	50.0 (18.0)
LV EF (biplane), % (SD)	54.5 (7.8)	55.1 (7.2)	55.7 (6.8)	54.6 (7.8)	53.3 (8.5)	54.0 (8.9)
LAVi, ml/m^2 (SD)	34.3 (12.0)	31.3 (8.6)	32.6 (9.8)	33.4 (11.3)	36.4 (12.7)	43.0 (19.4)
DT, ms (SD)	189.9 (58.0)	158.6 (37.3)	172.5 (40.7)	191.0 (53.0)	210.5 (68.6)	219.7 (71.5)
E/e′ ratio (SD)	8.0 (3.3)	6.3 (1.6)	7.0 (1.8)	7.9 (2.8)	9.1 (4.0)	11.3 (5.3)
E/A ratio (SD)	1.0 (1.6)	1.3 (0.4)	1.1 (0.3)	0.9 (0.3)	0.8 (0.4)	1.5 (6.4)
Myocardial GLS, % (SD)	− 16.3 (3.2)	− 17.4 (3.2)	− 17.1 (2.9)	− 16.3 (3.2)	− 15.5 (3.1)	− 15.7 (3.6)
Myocardial GLS, % (SD) Men	− 15.3 (2.9)	− 15.7 (2.7)	− 16.0 (2.8)	− 15.4 (2.9)	− 14.9 (2.8)	− 14.2 (3.6)
Myocardial GLS, % (SD) Women	− 17.2 (3.2)	− 18.5 (3.1)	− 17.9 (2.8)	− 17.1 (3.2)	− 16.1 (3.2)	− 16.9 (3.0)

The Tromsø Study (2015–2016)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVMMi* left ventricle myocardial mass index, *LV EF* left ventricle ejection fraction, *LAVi* left atrial volume index, *DT* mitral peak E deceleration time, *E/e′ ratio* mitral peak E to tissue Doppler peak e′ ratio, *E/A ratio* mitral peak E to peak A ratio, *GLS* global longitudinal strain, *MI* myocardial infarction, *HF* heart failure, *Afib* atrial fibrillation, *mMRC* modified Medical Research Council (mMRC) breathlessness/dyspnea scale, *SD* standard deviation. Due to missing observations, numbers (n) for the variables may be marginally less (within 1.0%)

Abnormal myocardial GLS in The Tromsø 7 Study sample

With the use of mean myocardial GLS values in the healthy individuals aged 40–99 years, myocardial GLS LLN equaled − 10.6% for men and − 11.7% for women. Data shown in Table 3 estimates LLN with bootstrapped 2.5th and 97.5th CI by age groups and sex. A tendency of declining LLN with the age was still present in both men and women, however the differences were non-significant (p-values for age trend were 0.522 and 0.801 for men and women respectively).

Abnormal myocardial GLS and risk factors

We estimated OR for factors possibly associated with abnormal myocardial GLS (Table 4). Individuals with diabetes had 2.91-fold (95% CI 1.52, 5.55) increased risk of having abnormal myocardial GLS. All other predictors had significant effect on abnormal GLS excluding hypertension and mMRC scale ≥ 2. Table 5 shows the difference in GLS for each of the significant predictors of GLS. The lowest myocardial GLS (SD) of − 14.3 (3.5) % was found in individuals with self-reported HF.

Myocardial GLS and SBP

Myocardial GLS in women declines as SBP increase (Fig. 3). In men with and without antihypertensive treatment differences in myocardial GLS between SBP groups were non-significant (p = 0.206 and p = 0.276 for untreated and treated men respectively). Men and women with BP treatment had lower values of myocardial GLS than those

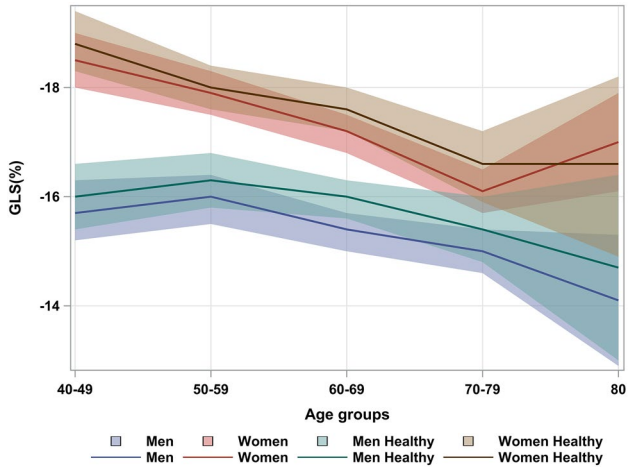

Fig. 2 Age and sex-specific myocardial GLS means with 95% CI bands in general and healthy subsamples (n = 1747). The Tromsø Study (2015–2016). For "General" subsample: p-value (Difference between men and women by age groups): 40–49: $p < 0.001$; 50–59: $p < 0.001$; 60–69: $p < 0.001$; 70–79: $p < 0.001$; 80+: $p < 0.001$. p-value (for change of mean myocardial GLS by age) Men: $p < 0.001$; Women: $p < 0.001$. Numbers for men and women: 40–49 (M99; W144) 50-59 (M144; W188) 60–69 (M314; W345) 70–79 (M200; W225); 80 + (M39; W49); Total n = 1747. For "Healthy" subsample: p-value (difference between men and women by age groups) 40–49: $p < 0.001$; 50–59: $p < 0.001$; 60–69: $p < 0.001$; 70–79: $p = 0.009$; 80+: $p = 0.115$. p-value (for change of mean myocardial GLS by age) Men: $p = 0.001$; Women: $p < 0.001$. Numbers for healthy: 40–49 (M81; W119); 50–59 (M109; W155); 60–69 (M170; W230); 70–79 (M72; W98); 80 + (M19; W15); Total n = 1068. *GLS* global longitudinal strain, *CI* confidence interval

Table 2 Healthy individuals (%) by age groups and sex

Age group (years)	Proportion of healthy[a] individuals	
	Men n/total (%)	Women n/total (%)
40–49	81/99 (81.8)	119/144 (82.6)
50–59	109/144 (75.7)	155/188 (82.5)
60–69	170/314 (54.1)	230/345 (66.7)
70–79	72/200 (36.0)	98/225 (43.6)
80+	19/39 (48.7)	15/49 (30.6)
p for trend	< 0.001	< 0.001

The Tromsø Study (2015–2016)

[a]Healthy individuals: all excluding those with hypertension, diabetes, atrial fibrillation, heart failure, angina, myocardial infarction, stroke, chronic bronchitis and ejection fraction of the left ventricle < 50%

without treatment. In linear regression analysis adjusted for age and sex, 10 mm Hg increase of SBP resulted in a 0.2% decrease of myocardial GLS ($\beta = 0.235$; $p < 0.001$). After adjustment for age, sex, BMI, history of: MI, atrial fibrillation, angina, diabetes, stroke, arterial hypertension and breathlessness scale, SBP remained an independent predictor of myocardial GLS decline ($\beta = 0.146$; $p < 0.001$).

Table 3 LLN for myocardial GLS expressed as percentage (95% CI)

Age group (years)	Men		Women	
	LLN (%)	95% CI[a]	LLN (%)	95% CI[a]
40–49	− 10.9	− 12.0, − 10.1	− 12.7	− 14.2, − 11.5
50–59	− 11.0	− 11.9, − 9.9	− 12.7	− 13.7, − 11.6
60–69	− 10.9	− 11.6, − 10.3	− 11.5	− 12.4, − 10.7
70–79	− 10.5	− 11.5, − 9.5	− 10.1	− 11.5, − 8.7
80+	− 7.8	− 11.0, − 5.4	− 10.9	− 13.8, − 9.0
All ages (40–99)	− 10.7	− 11.2, − 10.2	− 11.7	− 12.2, − 11.2
P for trend	0.522		0.801	

The Tromsø Study (2015–2016)

LLN lower limit of normal, *GLS* global longitudinal strain, *CI* confidence interval

[a]95% confidence intervals were calculated using bootstrapping with 1000 samples

Table 4 Odds ratios for factors associated with abnormal myocardial GLS

Parameter	Odds ratio (models with various predictors[a])		
	Point estimates	Wald 95% CI limits	p-value
Diabetes	2.91	1.52, 5.55	**0.001**
BMI, kg/m^2	1.23	1.17, 1.29	**< 0.001**
Angina	2.68	1.24, 5.80	**0.012**
MI	2.47	1.24, 4.96	**0.011**
Atrial fibrillation	2.04	1.02, 4.06	**0.043**
Stroke	2.67	1.11, 6.43	**0.029**
Hypertension	1.52	0.96, 2.39	0.072
mMRC scale ≥ 2	1.93	0.81, 4.59	0.138

The Tromsø Study (2015–2016)

[a]For each risk factor the OR for having an age and sex-specific abnormal GLS was estimated in a separate model

n of observations used 1746; Abnormal myocardial GLS (n = 100), Normal myocardial GLS (n = 1646)

BMI body mass index, *MI* myocardial infarction, *GLS* global longitudinal strain, *mMRC* scale modified Medical Research Council breathlessness/dyspnea scale

Subclinical HF and myocardial GLS

In the subgroup without LV echocardiographic abnormalities (total n = 709), 120 (29.1%) of women and 100 (33.8%) of men were categorized as SAHF individuals. Mean myocardial GLS (SD) (n) in those with SAHF were − 16.7 (2.5) % (n = 220) and − 17.9 (2.6) % (n = 489) in participants without SAHF ($p < 0.001$). In the SAHF positive group 3.2% reported dyspnea by exertion (mMRC scale ≥ 2, versus 1.6% in individuals without SAHF ($p = 0.257$).

Table 5 Mean myocardial GLS (SD) (95% CI) (n) adjusted for age and sex according to the history of the different risk factors

HF risk factors (total n = 1747)	Mean GLS (SD) (95% CI) (n)		p-value
	Present	Absent	
Self-reported HF	− 14.3 (3.5) (− 15.1; − 13.4) (51)	− 16.4 (3.1) (− 16.6; − 16.3) (1696)	< 0.001
Diabetes	− 14.8 (3.2) (− 15.4; − 14.2) (101)	− 16.5 (3.1) (− 16.6; − 16.3) (1646)	< 0.001
mMRC scale ≥ 2	− 14.8 (3.5) (− 15.5; − 14.1) (69)	− 16.5 (3.1) (− 16.6; − 16.3) (1678)	< 0.001
MI	− 15.2 (3.1) (− 15.8; − 14.6) (95)	− 16.5 (3.2) (− 16.6; − 16.3) (1652)	< 0.001
Angina	− 15.5 (3.5) (− 16.3; − 14.8) (70)	− 16.4 (3.1) (− 16.6; − 16.3) (1677)	0.017
Hypertension	− 15.9 (3.0) (− 16.1; − 15.6) (487)	− 16.6 (3.2) (− 16.8; − 16.4) (1260)	< 0.001
Stroke	− 15.8 (3.3) (− 16.6; − 15.0) (52)	− 16.4 (3.2) (− 16.5; − 16.3) (1695)	0.138
Atrial fibrillation	− 15.9 (3.3) (− 16.5; − 15.4) (112)	− 16.4 (3.2) (− 16.6; − 16.3) (1635)	0.090

The Tromsø Study (2015–2016)

GLS global longitudinal strain, *MI* myocardial infarction, *HF* heart Failure, *mMRC scale* modified Medical Research Council breathlessness/dyspnea scale, *CI* confidence interval, *SD* standard deviation

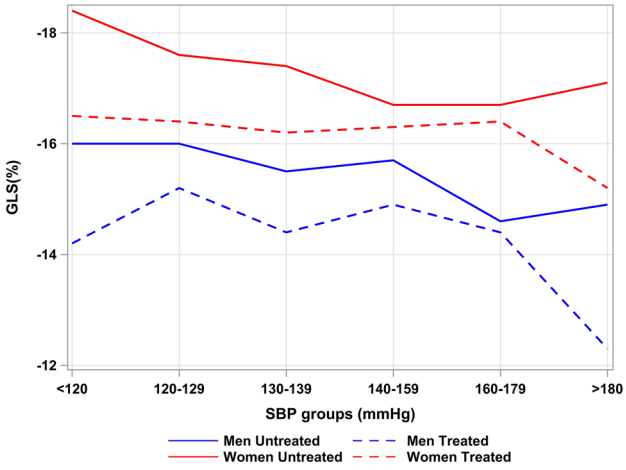

Fig. 3 Mean myocardial GLS levels stratified by SBP, sex and antihypertensive treatment. The Tromsø Study (2015–2016). Means are adjusted for age and estimated for a mean age of 63 years using linear regression. p-value between SBP groups: Men (Untreated) = 0.206; Women (Untreated) < 0.001; Men (Treated) = 0.276; Women (Treated) = 0.898. *SBP* systolic blood pressure; *GLS* global longitudinal strain, *SD* standard deviation

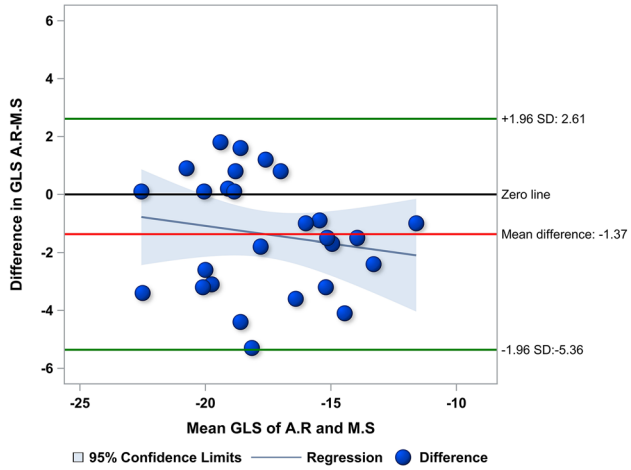

Fig. 4 Bland-Altman plot for inter-observer study. The Tromsø 7 Study. Difference in GLS: difference between observer AR and observer MS measurements (AR minus MS); [b]Mean GLS: mean GLS of two observers AR and MS; SD: standard deviation; GLS: Global longitudinal strain; AR: observer 1; MS: observer 2. *P-value for linear regression model [y (difference in GLS) = × (mean GLS)] = 0.408

Inter-observer variability of GLS

We benchmarked the single reader (MS) against another clinical echocardiographist (AR) who had extensive experience of routine measurement of myocardial GLS. Analyses of myocardial GLS reproducibility (Online Resource 1) and Bland–Altman plots visual assessment (Fig. 4) showed good to excellent intra- and inter-observer agreement levels.

Discussion

This is the first study to our knowledge to explore GLS patterns and its associations to CVD risk factors and SAHF in a general population. The main results of this study were the following: (1) mean GLS in healthy participants aged 40–99 years was − 15.9 (2.7) % in men and − 17.8 (3.1) % in women with significant change of GLS by age in both sexes; (2) GLS LLN was estimated as − 10.6% for men and − 11.7% for women aged 40–99 years; (3) GLS declines in women with increase of SBP; (4) Increase of SBP by 10 mm Hg results in 0.2% GLS reduction in age and sex adjusted regression model; (5) Myocardial GLS in

individuals with SAHF was 1.2% lower ($p < 0.001$) than in participants without SAHF.

Myocardial GLS in general population

Our findings of a decline in myocardial GLS with age confirmed previous studies describing the same age and sex related myocardial GLS patterns [15, 33]. However, there was a number of controversial reports with no detected myocardial GLS age change in general or healthy samples [34–36]. Additionally, we found that change in myocardial GLS by age disappears in men when individuals with echo abnormalities were excluded from the "healthy" subgroup.

Mean myocardial GLS ± SD values derived from averaging of endo- mid- and epicardial layer's GLS values in healthy participants in The Tromsø 7 Study sample were similar to those published in Dalen et al. work (− 15.9 ± 2.3% in men and − 17.4 ± 2.3% in women) based on data of 1266 healthy individuals participated in HUNT study of Norway [37]. However, other authors found significantly higher absolute values of mean myocardial GLS in healthy subjects. One of the possible reasons of different GLS values found in healthy individuals among the studies is the use of the different myocardial layers (endo- midwall or epicardial layer) for calculating the GLS since recent reports show endocardial GLS approximately 30% higher than epicardial GLS [35]. In the guidelines GLS level of − 20% is considered as the borderline in healthy subjects [13]. Guideline based GLS LLN values by vendor (GE Software) were higher than values we found. It is also important that myocardial GLS values of our study were derived using EchoPac version (EchoPac ver. 113) which was newer than these listed in the guidelines [13]. Castel et al. reported that upgrades of speckle tracking software were associated with significant changes in GLS values [38]. It is worth to mention that sample sizes in HUNT and Tromsø studies were much larger than in the other studies. Thus, Alcidi et al. reported myocardial GLS ± SD level of − 22.7 ± 1.8% in a sample of 266 healthy individuals [15]. The authors found significant change of myocardial GLS by age even though the participants age (mean ± SD) was 39.2 ± 17.5 years compared with 63.0 ± 10.8 in Tromsø 7 population sample.

Taking into the account the small sample size of "healthy" individuals in higher age groups, we assessed bootstrapped 95% CI for myocardial GLS LLN. We found no significant change of LLN by age neither in men nor women.

Our results indicate that subclinical myocardial dysfunction assessment should not be limited to considering hypertension alone, as myocardial GLS is influenced by other comorbidities and risk factors as well. We found that BMI was associated with presence of myocardial GLS below LLN. It was consistent with previous research of Bendiab et al. [39] where most of the risk factors were inversely correlated with myocardial GLS. The BMI has been described as an independent factor for low myocardial GLS, previously [39]. However, the associations between myocardial GLS and self-reported dyspnea symptoms are more complicated. Relatively low myocardial GLS (SD) − 14.8 (3.5) % in those with mMRC scale ≥ 2 can be explained by the characteristics of the selected sample and association of abnormal myocardial GLS with diastolic dysfunction and LV filling pressures [40]. Another explanation of the low myocardial GLS levels in patients with dyspnea could be the unrecognized systolic dysfunction which prevalence according to earlier reports reaches 15.7% (95% CI 12.9–19.0) in individuals aged 65 years or older [41].

Myocardial GLS and BP

In our study we tried to expand the current knowledge about factors contributing to myocardial GLS decline. SBP was chosen as such as a factor due to its known association to myocardial GLS in different patient groups [16] and the high prevalence of arterial hypertension worldwide. Another important aspect is that myocardial GLS decline in hypertensives reflects subclinical damage of LV structure and function due to early microscarring of the subendocardium, especially in the highly hypertrophied muscles [42]. Furthermore, increased afterload is known to prolong contraction and delay active relaxation [43] and reduce longitudinal strain and strain-rate [44].

We have found mean myocardial GLS decline up to − 15.9% in patients with arterial hypertension. This value was higher than GLS LLN in both men and women with the significant difference with those without arterial hypertension (GLS = − 16.6%, $p < 0.001$). Adjusted for age and sex 10 mm Hg SBP increase was responsible for 0.2% of myocardial GLS decrease. This confirmed the association between SBP and myocardial GLS found in earlier studies [39].

We assessed the sex-related LV function in hypertensive individuals. Previous reports have found contradicting results [45]. We found that in women myocardial GLS declined from − 18.4% in SBP group of < 120 mm Hg to − 17.1% in those within SBP > 180 mm Hg ($p < 0.001$). We revealed a similar decline among men, however without significant difference between SBP groups. Presumable cause could be the small number of men with the highest SBP levels (only 9 persons in the SBP > 180 mm Hg group). Mean myocardial GLS was lower in the high-normal SBP group of 130–139 mm Hg compare to normal SBP groups in both men and women, showing that longitudinal function of LV was already impaired in these groups of study participants. The previous report by Tadic et al. showed that myocardial GLS was lower in high-normal BP individuals with no such BP effect on radial LV function [46]. We revealed

that women have larger values of myocardial GLS in both healthy individuals as well as in those with CVD risk factors. Partly it could be explained by pathophysiological diversities between men and women reflected in complex relationships between LV mechanics and sex hormones. Thus, Salem et al. showed that higher levels of testosterone in men were associated with decreased myocardial GLS [47].

It is worth to mention that hypertensive individuals are characterized by increased afterload which leads to thickening of the LV wall and LV hypertrophy development [48] as a compensatory mechanism. Some studies demonstrated that decreased longitudinal systolic function cannot be attributed to the afterload increase in patients with arterial hypertension and LV hypertrophy [49], which might be due to low effect of increased blood-pressure on the compensatory hypertrophied ventricle, where the smaller ventricle and thicker walls lead to reduced wall stress. Kim at al. in a study of 145 hypertensive patients [11] showed that different ventricular regions have different susceptibility for stress induced afterload with inhomogeneous development of ventricular hypertrophy. Myocardial GLS has been shown to be lower in ventricular regions with more pronounced LV hypertrophy. Concerning the fact that in our study sample individuals with 70+ years of age had mean LVMMi > 47 g/$m^{2.7}$, we assume that arterial hypertension exerts its negative influence on myocardial GLS through microscarring and insufficient myocardial perfusion in LV hypertrophy.

Myocardial GLS and SAHF

Identification of individuals with SAHF who are at risk of developing advanced HF stages appears to be a promising CVD primary prevention strategy. In most of the cases patients without symptoms are rarely involved in screening procedures until development of later HF stages. In our study we found that mean GLS (SD) in individuals with SAHF − 16.7 (2.5) % was lower compared to those without − 17.9 (2.6)% ($p < 0.001$). The components defining SAHF (elevated SBP, diabetes, obesity or atherosclerosis) were found to be associated with abnormal GLS, possibly indicating the presence of subclinical damage of the myocardium [20, 21]. It is worth to mention that myocardial GLS may have benefits in early HF detection because symptoms of HF are not always present in even more advanced HF stages (Stage B HF). Thus, Redfield et al. reported that 14% of patients with dilated cardiomyopathy and LVEF < 50% had never experienced any of HF symptoms [50].

Myocardial GLS and vendor-specific software

Different vendor-specific image postprocessing algorithms were earlier considered as an issue which could potentially limit clinical use of the strain imaging [51]. However, launching of EACVI/ASE Strain Standardization Task Force [30] resulted in increased number of evidence on improvement of concordance in strain imaging between vendors [52]. Yingchoncharoen et al. reported no significant difference of GLS variability in healthy individuals between EchoPac and non-EchoPac software ($p = 0.98$) [16]. Based on these findings we assume that values of myocardial GLS in healthy population of our study is valid not only for EchoPac but also for another vendor's software.

Strengths and limitations

This is a large population-based study with a large age range providing a good power to estimate the normal range of normal strain values. Strain is reduced with increasing afterload. Possible use of afterload adjustment for example, indexing myocardial GLS to the population-based average BP may solve the issue, however data on SBP and DBP during echo examination in The Tromsø 7 Study is lacking. Single center study design could be a possible source of reduced validity of the findings. Another limitation is the low sample size above 80 years of age. Data on use of cardiotoxic drugs is not available in The Tromsø Study and accordingly not included as risk factor in SAHF definition.

Clinical implications

The results we demonstrated could potentially be used in control of the patients with SAHF with help of GLS monitoring over time. Age-related GLS LLN is a promising parameter for clinical follow-up in group of patients with subclinical HF due to its sensitivity for early myocardial function impairment.

Conclusions

In large unselected samples from the general population myocardial GLS values were found both in the total and healthy subsamples. Mean myocardial GLS declined with age in both sexes in general and in healthy participants. SBP increase was associated with GLS decline in women. GLS was decreased in subjects with subclinical HF. The close association of GLS to SAHF parameters indicates its importance for subclinical heart disease diagnostics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have conflict of interest.

Ethical approval The Tromsø Study protocol was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2014/940/REK Nord) and was performed according ethical standards outlined in the 1964 Declaration of Helsinki.

Informed consent All participants of the study provided signed informed consent.

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Online Resource 1 Intra and Inter-observer variability of myocardial GLS. The Tromsø Study (2015-2016).

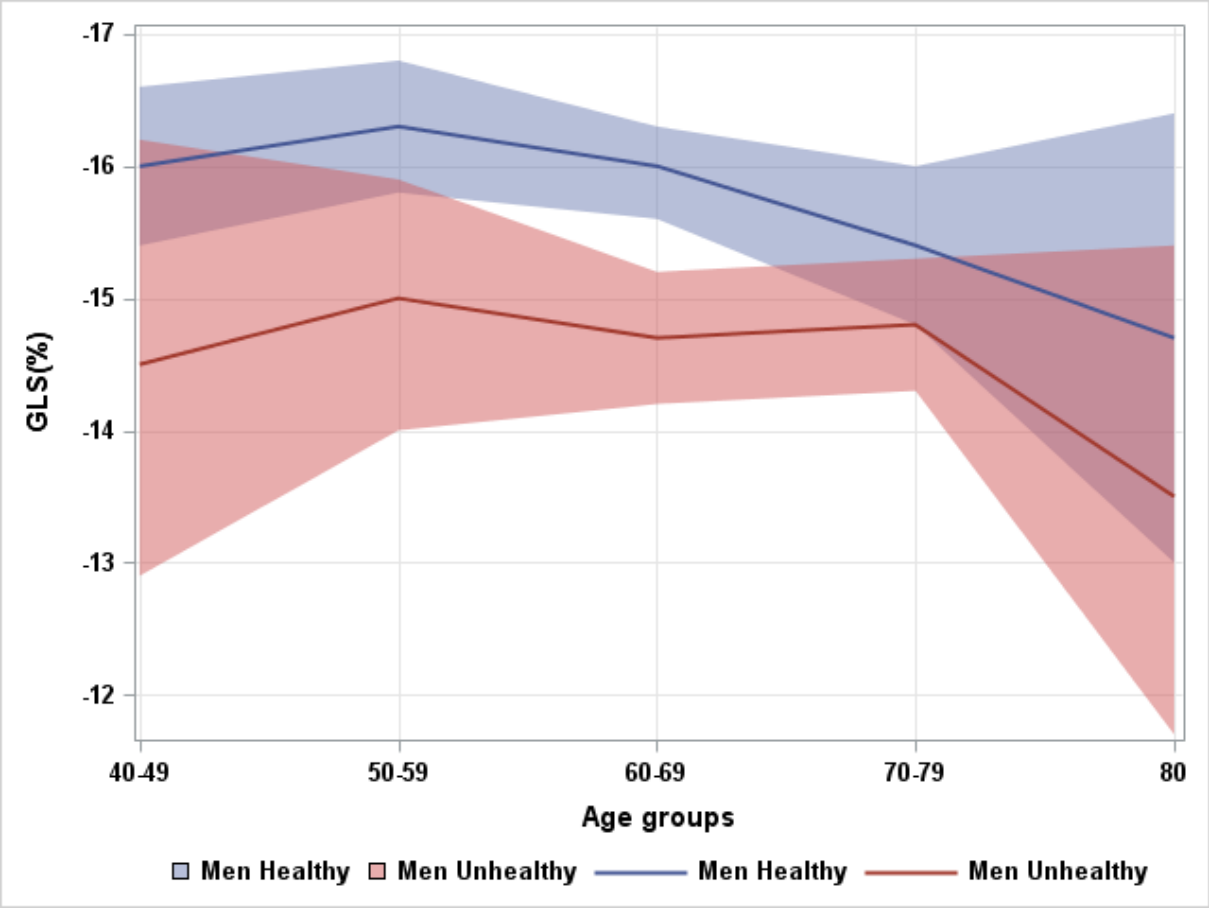
Intra-observer variability[b]			Inter-observer variability[c]		
ICC (95% CI)	Mean difference between observers (SD) (p for difference)	CR	ICC (95% CI)	Mean difference between observers (SD) (p for difference)	CR
0.96 (0.89-0.98)	0.53 (2.02) (p=0.274)	5.60	0.82 (0.47-0.93)	-1.37 (1.99) (p=0.001)	5.51

[a]GLS: global longitudinal strain; ICC: intraclass correlation; SD: standard deviation; CI: confidence interval; CR: coefficient of repeatability

[b]Measurements were made by the same observer (M.S) with 3-months interval in between.

[c]Measurements made by A.R and M.S

Online Resource 2 Age and sex-specific myocardial GLS means with 95% CI bands in healthy and unhealthy men (n=796). The Tromsø Study (2015-2016)

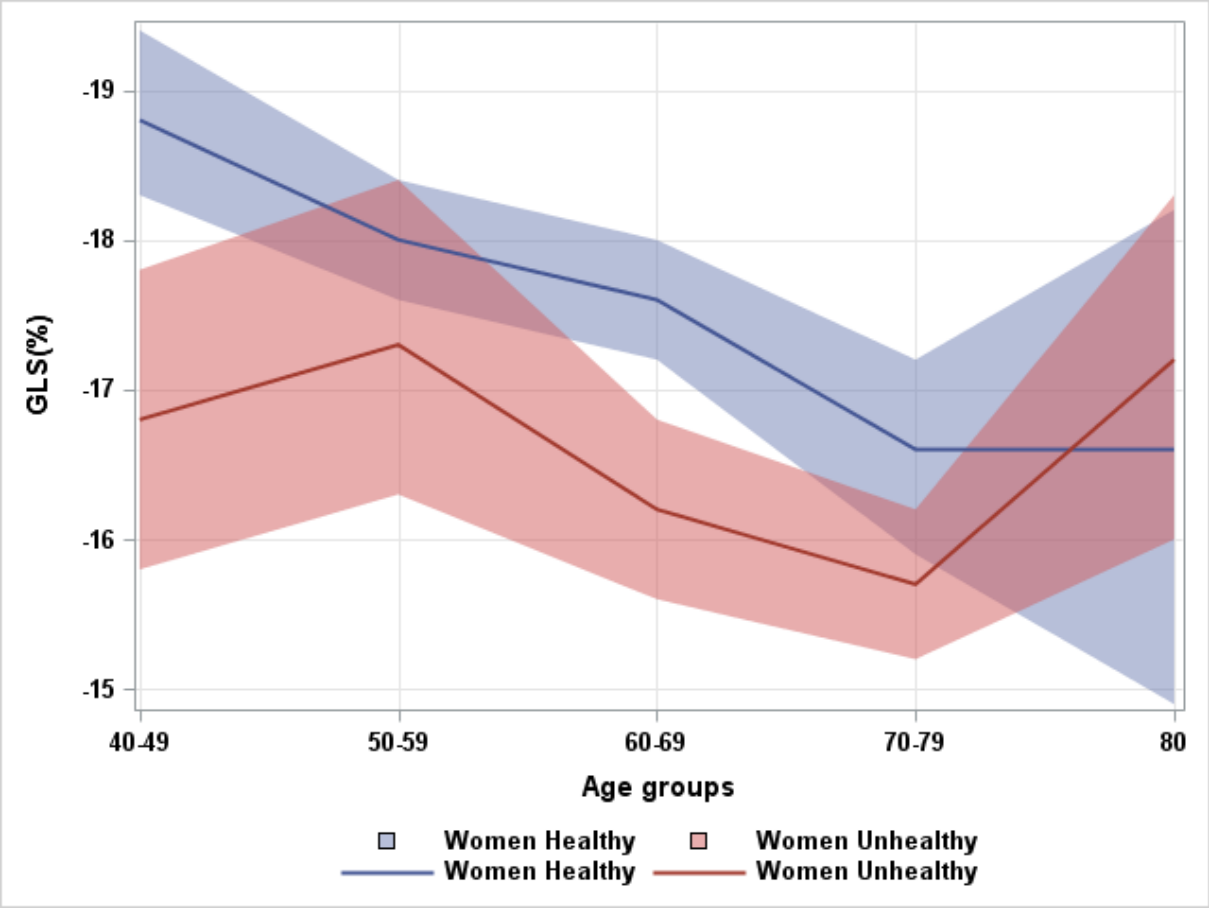


*p-value (Difference in GLS between healthy and unhealthy men by age groups): 40-49: p=0.041; 50-59: p=0.013; 60-69: p<0.001; 70-79: p=0.119; 80+: p=0.325

*p-value (for change of mean myocardial GLS by age) Healthy men: p=0.001; Unhealthy men: p=0.070

[a]GLS: Global longitudinal strain; CI: confidence interval

Online Resource 3 Age and sex-specific myocardial GLS means with 95% CI bands in healthy and unhealthy women (n=951). The Tromsø Study (2015-2016)



*p-value (Difference in GLS between healthy and unhealthy women by age groups): 40-49: p=0.002; 50-59: p=0.219; 60-69: p<0.001; 70-79: p=0.033; 80+: p=0.529

*p-value (for change of mean myocardial GLS by age) Healthy women: p<0.001; Unhealthy women: p=0.070

[a]GLS: Global longitudinal strain; CI: confidence interval

Online Resource 4 Healthy and unhealthy individuals with measured mean myocardial GLS according to age and sex. The Tromsø Study (2015-2016)

Age (y)	40-49	50-59	60-69	70-79	80+	Total (n)
Healthy men (n)	81	109	170	72	19	451
Unhealthy men (n)	18	35	144	128	20	345
Healthy women (n)	119	155	230	98	15	617
Unhealthy women (n)	25	33	115	127	34	334

[a]GLS: Global longitudinal strain

Paper III
[Manuscript]

Prediction of chronic heart failure and COPD in a general population. The Tromsø Study

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Abstract

Aim. Heart failure (HF) and chronic obstructive lung disease (COPD), the main causes of dyspnea, is diagnosed with echocardiography and spirometry. Our aim was to determine the prevalence of HF and COPD in a general population and to what extent their clinical characteristics differ.

Methods and results. In the 7th survey of Tromsø study (2015-16) 1538 subjects aged 40 years or more were examined with echocardiography, spirometry, lung sound recordings, questionnaires, and NT-proBNP analysis. A diagnosis of heart failure (HFrEF, HFmrEF, or HFpEF) or COPD was established according to current guidelines. Predictors of HF and COPD were evaluated by logistic regression.

Age standardized prevalence of HF was 6.8% for women and 6.1% for men, the respective figures for COPD were 5.2% and 5.1%. Among 139 subjects fulfilling the HF criteria, 17.1% reported to have the disease, whereas 31.6% reported COPD of those fulfilling COPD criteria. Shortness of breath at exertion was the strongest predictor of HF; 59% of those with mMRC ≥2 had HF and 24% had COPD. Current smoking was the strongest predictor of COPD, but did not predict HF. Basal inspiratory crackles was a significant predictor of HF in multivariable analysis. Clinical scores based on history, symptoms and signs predicted HF and COPD with AUCs of 0.833 and 0.829, respectively.

Conclusion. Study participants with HF and COPD were most often not aware of their condition. Shortness of breath was the strongest predictor of HF, smoking of COPD, while less emphasis should be laid on crackles and wheezes.

Keywords: Epidemiology, Heart failure, Chronic obstructive pulmonary disease, Spirometry, Echocardiography, symptoms, identification, biomarkers

Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are two of the more common chronic diseases and are leading causes of morbidity and mortality worldwide with high social and economic negative impact. Exacerbations of heart failure and COPD are major causes of admittance to emergency departments.(1, 2) HF and COPD are not curable diseases, but early diagnosis can lead to preventive measures, including smoking cessation,(3) that can prolong life and reduce the number of acute exacerbations.(2, 4)

HF and COPD might be under-diagnosed at an early stage partly due to unspecific early symptoms.(5) A cardinal symptoms for heart failure, exertional dyspnea,(6) is also shared by COPD, and also cough may be present in both diseases.(7) HF and COPD may overlap, and increasingly by age.(8, 9)

Clinicians take chest signs like crackles and wheezes into account when HF or COPD is suspected, but the sensitivity and specificity of these findings are regarded to be low.(6, 10) This study is based on the seventh survey of the Tromsø Study where recording of lung sounds was included among the clinical investigations.(11)

The aim of this study was to determine how abnormal lung sounds and respiratory symptoms, shortness of breath in particular, may predict HF and COPD, as identified by current guidelines and to what extent the occurrence of these diseases overlap in a general population.

Methods

Study population

The Tromsø study was established in 1974 with the main aim of understanding the role of modifiable CVD risk factors. Seven waves of the study have been carried out with the last health survey performed in 2015-16. Main features of the methodology and study design has been described previously.(12) In

this cross-sectional study, our sample consists of randomly selected participants attending the second visit of the seventh survey of the Tromsø study (Tromsø 7), between May 2015 and October 2016. All Tromsø residents 40 years and older (n=32 591) received a postal invitation to participate in the first visit of Tromsø 7. A random sample was selected for the second visit including 20% of those aged 40-59 years and 60% of those aged 60-84 years, and, among these, those who attended the first visit were invited. In addition, individuals who had participated in echocardiography in previous surveys of the study were invited to obtain repeated measurements.

Data Collection

The following information on participant´s diseases and risk factors was retrieved from self-administered questionnaires at the first visit: myocardial infarctions (MI), angina, atrial fibrillation, arterial hypertension, diabetes, COPD, and asthma. Smoking was categorized as never smoked, previous and current smokers, and the participants answered the question "Do you cough about daily for some periods of the year". At the second visit, before spirometry, the participants answered modified Medical Research Council questionnaire (mMRC) on dyspnoea.(13) Dyspnoea was further characterized using the question: "How is your breathing today compared to normal?". Serum levels of NT-proBNP and C-reactive protein (CRP) were measured with reagents from Roche Diagnostics, Norway. The age related reference values of NT-proBNP (97.5 percentile in a healthy population) was provided by Roche Diagnostics, Norway (Appendix).

Echocardiographic assessment was performed by an experienced echo technician using a GE Vivid E9 scanner (GE Medical, Horten, Norway). Echopac version 113 (GE Medical, Horten, Norway) was used for offline image reading performed by M.S.

Ultrasound examination was performed according to guidelines(14) in the left lateral decubitus position. Left ventricular (LV) myocardial mass was calculated based on M-Mode images with the use of following formula: LV Mass (g) = $0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6$ where LVEDD

is LV end-diastolic diameter, IVSd is interventricular septum thickness in diastole, PWd is LV posterior wall thickness in diastole LV ejection fraction (EF) and left atrial (LA) volume were calculated using biplane Simpson's method. LV myocardial mass index (LVMMi) was estimated by normalizing LV mass and to height raised to allometric power of 2.7. LA volume index (LAVi) was estimated by normalizing LA volume to BSA. BSA was calculated by the Du Bois formula (BSA = [weight {kg} 0.425 × height {cm} 0.725] × 0.007184).(15) LA enlargement was considered in those with LAVi >34 ml/m^2; LVH was defined in men with LVMMi >50 g/$m^{2.7}$ and women with LVMMi >47 g/$m^{2.7}$.(14)

Mitral valve Doppler measurements (mitral inflow E wave) were performed at the tip of the mitral leaflets in the apical 4-chamber view. We kept the insonation angle for Doppler measurements perpendicular toward the mitral inflow. Tissue Doppler derived parameters such as peak septal and lateral e´ were obtained from apical 4-chamber view with 5-mm sample volume located at the septal and lateral side of the mitral annulus. Echo markers of diastolic dysfunction in individuals with normal LVEF were following: average E/e´ >14; septal e´ velocity <7 cm/s or lateral e´ velocity <10 cm/s; Tricuspid regurgitation velocity >2.8 m/s; LAVi >34 ml/m^2.

Spirometry was performed using SensorMedics Vmax 20c Encore (VIASYS Healthcare Respiratory Technologies, Yorba Linda, CA, USA). Calibration was done daily. We followed the standards of the American Thoracic Society (ATS)/ European Respiratory Society (ERS).(16) Tests with FEV1<0.3 litre and with expiration lasting less than 3 seconds were regarded invalid. Post-bronchodilator measurements were not carried out. We used the Global Lung Function Initiative (GLI 2012) as a reference with the 5th percentile among healthy never smokers as lower limit of normal (LLN).(17) We registered arterial oxygen saturation ($Sp0_2$) with a pulse oximeter Onyx II model 9550 (Nonin Medical, Inc., Plymouth, MN, USA) after resting 15 minutes. The highest value after three measurements was registered. Medication for asthma and COPD should be taken as usual.

Lung sounds were recorded at six locations of the chest, 15 seconds at each site, with a Sennheiser microphone inserted in the tube of a Littmann Classic II stethoscope. Presence of wheezes and crackles (also called rales or crepitations) during inspiration and expiration was determined by clinicians independently classifying the recordings blinded for other information; details on recording sites and classification of the sounds have recently been published.(11) Basal inspiratory crackles heard bilaterally was a category used in the analysis.(18)

Definition of HF and COPD

HF was defined according to the latest European Society of Cardiology (ESC) guidelines(2) into three types: Heart failure with reduced ejection fraction (HFrEF) characterized by left ventricular ejection fraction (LVEF) <40% and presence of dyspnea (mMRC ≥1); Heart failure with mid-range ejection fraction (HFmrEF) with LVEF 40-49%, dyspnea, serum NT-proBNP >125 pg/mL and any of the following: structural heart disease/diastolic dysfunction; Heart failure with preserved ejection fraction (HFpEF) with LVEF ≥50%, dyspnea, serum NT-proBNP >125 pg/mL and any of the following: structural heart disease/diastolic dysfunction.

Structural heart disease included left ventricle hypertrophy (LVH) and/or left atrial (LA) enlargement. Diastolic dysfunction was defined by joint European Society of Cardiovascular Imaging and American Society of Echocardiography guidelines.(19)

A diagnosis of COPD was established when forced expiratory volume in one second (FEV_1)/Forced ventilator capacity (FVC) was lower the normal (LLN, the 5% percentile in a healthy non-smoking population), and the participant had answered yes to the question “do you get short of breath when hurrying on a level surface or walking up a slight hill “ (mMRC=1 or higher) or to the question “do you cough about daily for some periods of the year”.(20)

Sensitivity analysis

Evaluation of predictors of HF and COPD was mainly done in subjects classified for both diagnoses. In addition we evaluated HF predictors in all subject that could be classified according to the HF criteria and likewise COPD predictors in all subject that could be classified according to COPD criteria.

Statistical methods

Crude prevalences were standardized for age and gender using the population distribution from the Tromsø municipality of 1st January 2019. Frequency of characteristics were determined according to HF and COPD status and by type of HF, and differences between groups were analyzed by Chi-square statistics. Predictors of HF (irrespective of COPD co-morbidity) and COPD (irrespective of HF co-morbidity) were evaluated by logistic regression, adjusted for age, and relevant explanatory variables associated with outcome with a p-value <0.1, were entered the multivariable analyses. ROC curves evaluating predictive value of variable from history, symptoms signs, and biomarkers were produced based on output from the multivariable analysis. SPSS statistical software version 26 (IBN, Armonk, NY, USA) was used. Visual assessment of overlap between HF, COPD, and mMRC ≥2 was made using a Venn diagram (R package version 6.0.0.).

Ethical considerations

The Tromsø study protocol was performed in accordance with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2014/940/REK Nord). Written consent was provided by all study participants.

Results

Inclusion of participants in the analyses is shown in Figure 1. Out of 7316 attending the spirometry, valid measures were obtained in 7247 with a mean age of 63.0 years (range 40-84 years). Among these, 7110 answered the mMRC questionnaire and the question on cough, and a COPD diagnosis could be made in 432 (6.1%). Age standardized prevalence of COPD was 5.1 % for men and 5.2% for women. Echocardiography was done in 2340 participants, 2106 of these also attended spirometry. Evaluation of EF could be done in 2007 subjects (Figure 1) and among these the mMRC questionnaire was answered and NT pro-BNP was analyzed in 1624 (mean age 64.0 years). A diagnosis of HF was established in 155 (9.5%). The age-standardized prevalence of HF was 6.1% for men and 6.8 % for women. Presence of both HF and COPD could be evaluated in 1538 participants (mean age 63.7 years), 51.5% were women and 48.5% were men. A diagnosis of COPD was established in 84 and HF in 139 participants, and 14 had both (Table 1, Figure 2). The prevalence of the diseases did not differ by sex, but significantly by age ($p<0.001$); 64.8% of the 125 subjects with HF and without COPD were aged 70 years or more compared to 28.8 % of those with COPD (Table 1). Of those with COPD, 23% had mMRC =0 with the diagnosis based solely on spirometry and periods of daily cough. Crackles were heard in one out of five subjects with HF or COPD, but basal bilateral crackles in only one out of twenty. Wheezes were heard more frequently in COPD than in HF (Table 1). High frequency of FEV_1 <LLN was found in both COPD and HF, and reached 64.3% in subjects with both COPD and HF. Increased levels of NT-proBNP was only found in the HF groups. SpO2 values between 92% and 100% were found, and an increased occurrence of SpO_2 ≤95% was mainly found among subjects with COPD (9%, $p=0.02$).

Prediction of HF and COPD

Age-adjusted ORs in predicting HF and COPD are shown in Table 2. Current smoking predicted COPD with an OR of 15.8, but was not associated with HF. Reporting mMRC ≥2 was a particular strong predictor of HF. As many as 59% of 71 participants with mMRC ≥2 had HF (OR 19.5), while 23.9% had COPD (OR 6.3) (figure 2). Reporting more shortness of breath than usual on the examination day predicted both HF and COPD. Basal bilateral inspiratory crackles, was associated with both diseases, but significantly only with COPD (in the univariable analysis), whereas hearing wheezes was a significant predictor of COPD only. Self-reported hypertension, atrial fibrillation, and myocardial infarction had ORs for HF between 3.2 and 5.4, but did not predict COPD. Self-reported heart failure was a strong predictor of HF, but was registered in only 17.1% of participants with an established HF. HF could be established in only 21 of the 47 participants with self-reported HF. Among those with an established COPD, 31.6% reported to have the disease (Table 1), but over-diagnosis was as common as for HF. COPD predicted HF with an OR of 1.97. NT-proBNP was a strong predictor of HF and not associated with COPD.

Multivariable analysis

In the multivariable analysis, basal bilateral inspiratory crackles became a significant predictor of HF, but not of COPD. ROC curves were produced based on the multivariable analyses, and the relative weight of the included predictors in the scores applied are shown in Figure 3. When assessing prediction of HF, self-reported heart failure was excluded, and an AUC of 0.833 (95% CI 0.790 – 0.875) was obtained. Including this variable gave similar ROC-curve (AUC = 0.829). When instead three levels of raised NT-proBNP (<125 pg/ml, ≥ 125 pg/ml - <97.5 percentile and ≥97.5 percentile, were included in the analysis, an AUC of 0.909 (95% CI 0.877 – 0.940) was found. When assessing predictors of COPD self-reported COPD was excluded and an AUC of 0.829 (95% CI 0.783 – 0.875) was found. When the variable self-reported COPD was included a nominally higher AUC of 0.840 was

found. SpO2 ≤95% and CRP ≥5 mg/L were not significant predictors of COPD in the multivariable analysis.

Sub-types of HF

The frequency of establishing the three categories of HF was 38.7% for HFrEF, 21.3% for HFmrEF, and 40% for HFpEF. The occurrence of HF-type varied significantly with age (p=0.003, Table 3 or Appendix A), HFrEF was the most frequent type in participants younger than 70 years while HFpEF was most frequent in those older than 70 years (Figure 4). For COPD without concomitant heart failure, only a slight, and statistically insignificant, increase in prevalence by age was observed (Table 1, Figure 4).

NT-proBNP >125 pg/ml was found in 58.3% of the subjects with HFrEF.

Sensitivity analysis

Only small and insignificant changes were found when predictors of HF were evaluated by univariable and multivariable logistic regression in a somewhat extended sample of 1624 subjects. When predictors of COPD were evaluated in a sample of 7110 subjects, we found that statistical associations became stronger for crackles and wheezes, but self-reported cardiovascular diseases and NT-proBNP were still not associated with COPD. SpO_2 ≤95% became more strongly associated with COPD with an OR of 3.5 (95% CI 2.3 – 5.4). ROC curves based on multivariable analysis in the extended samples did not change the AUC.

Discussion

Main findings

Our study indicates that HF should always be considered in patients reporting exertional dyspnoea when presenting in primary care, also in the presence of COPD. We found HF in as many as 59% of

the participants who reported to “walk slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level” (mMRC=2). The content of mMRC=2 corresponds rather closely to NYHA grade 3,(21) a scale mainly used for grading HF patients. We found a history of smoking to be the strongest predictor of COPD, but smoking status is already recognized as the most important information in early diagnosis of this disease.(20) We could confirm that crackles is a useful finding in the diagnosis of HF, but also frequently found in COPD. Hearing crackles (any or basal) was not a significant independent predictor of COPD in the multivariable analysis, which may partly be explained by frequent occurrence of crackles among current smokers.(11) Wheezes was confirmed to be an independent predictor of COPD.(22) ROC analyses showed that HF and COPD can be identified with similar ease based on history, symptoms, and signs. HF was most strongly predicted when information on NT-proBNP was included.

Comparison with previous studies

To our knowledge, the 2016 ESC guidelines have not previously been applied in population based studies. The distribution of the HF sub-types was similar to what found in a recent Danish study.(23) In a Swedish register based study, including a population aged 18 years or more, the prevalence of age standardized HF was less than 2%.(24) As only 40% had the diagnosis based on echocardiography this might have caused a significant under-diagnosis, especially in patients not requiring hospitalization where they are more likely to receive echocardiography. The Swedish figure is more comparable to the rate of self-reported HF in our study than the actual prevalence of HF, which is more than twice as high. We found a considerable underdiagnosis of HF, and one may question whether the 2016 ESC diagnostic criteria are sufficiently strict. Since the criteria for diastolic dysfunction has been sharpened, decreasing the prevalence in a general population from 30 to 3%, this is unlikely.(2) The prevalence of COPD (with FEV1/FVC <LLN instead of <0.7 as diagnostic criterion, like in our study) was 7.3 % in a Norwegian study from 2006-8.(25) The lower prevalence in

our study (6.2%) may be partly explained by the inclusion of respiratory symptoms as diagnostic criterion. Improved lung health due to drop in smoking after 2008 may also have played a role.

A combination of HF and COPD seems to be less frequent than previously reported. We found HF in 16.7% of those with COPD, while the corresponding frequency in a register-based study from Taiwan was 28.9%.(9) Among the subjects with HF in our study, we found COPD comorbidity in 10% only. In a Danish study, COPD was found in 35% of patients admitted with heart failure.(26) This discrepancy may be partly explained by selection of patients with severe disease in the Danish study. The use of fixed FEV_1/FVC ratio of 0.7 as criterion for COPD instead of LLN, which we used, has probably also contributed to a higher prevalence of COPD.(25) Several authors have warned against over-diagnosis of COPD in heart failure, since pulmonary congestion can lead to bronchial obstruction and a decreased FEV_1/FVC ratio.(5, 27, 28) The strict criteria for COPD in our study (FEV_1/FVC <LLN and symptoms) has probably made over-diagnosis less likely. The high frequency of coughing, smoking, FEV_1 <LLN, and self-reported COPD in the group with both diseases compared to those with HF only (Table 1), indicates that over-diagnosis of COPD in subjects with HF has been a minor problem.

Predictors of HF have often been evaluated in selected populations, like in emergency departments. Shortness of breath has been found to be of great importance in such settings.(6, 29) Roalfe and co-workers were not able to evaluate shortness of breath as a diagnostic clue in their study, since almost all patients referred from primary care for cardiologic evaluation had this symptom, and the symptom was not graded.(30) Crackles (crepitations) was found to be sufficiently discriminating to be included in a clinical prediction rule for HF, together with a history of myocardial infarction, leg oedema, and a natriuretic peptide test. In a larger study by Fonseca and co-workers from 2004, 1058 primary care patients with history, symptoms, or signs indicating HF were examined with echocardiography.(18) Shortness of breath was a strong predictor of HF, together with cardiovascular disease, like in our study. Crackles (basal rales) was more frequently registered and was more strongly associated with HF than in our study. One may question whether selection bias has led to

overrepresentation of patients with crackles in this study. Crackles tend to be more frequent when the HF gets more severe,(31) and registration of crackles in the study by Fonseca and co-workers might have been influenced by the degree of suspicion of HF.

In a recent study of 1088 patients with HFrEF or HFmrEF, 19% had NT-proBNP <125 pg/ml.(32) This is probably comparable to our results, with a frequency of 42% in the HFrEF group and, by definition, 0% in the HFmrEF group. HFrEF can, accordingly not be fully excluded with NT-proBNP<125 pg/ml, but with such low values the prognosis is good.(32)

Strengths and limitations

Tromsø 7 had a 65% response rate. The Tromsø Study has a high external validity for the Norwegian population,(12) but people with poor health might have found it difficult to participate and are probably underrepresented. We applied the new diagnostic criteria for heart failure, and reading of echocardiography was blinded for other information about the participants. Regarding the diagnosis of COPD, we included respiratory symptoms among the diagnostic criteria, which is now recommended in GOLD guidelines.(20) However, post-bronchodilator spirometry was not carried out, which might have led to over diagnosis in some participants.(33) Recorded lung sounds have not been applied in previous studies on prediction of HF and COPD. The classification of the sounds was also blinded, and an objective identification of lung sounds was thus made possible. We were not able to evaluate other clinical signs, such as oedema and neck-vein distension. Relying on self-report for previous diseases introduces the limitation of recall bias.

Conclusion

The study indicates that a doctor may identify HF and COPD, and also differentiation between the diseases, based on history, symptoms, and signs. Shortness of breath and abnormal lung sounds may be found in both diseases, previous cardiovascular disease points at HF, while a history of smoking

points at COPD. Wheezes were independent predictors of COPD, while NT-proBNP was not associated with COPD. However, echocardiography and spirometry are needed for verification of the diagnoses.

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Conflict of interest

Dr. Schirmer reports grants from Novartis, grants and personal fees from Astra Zeneca, personal fees from MSD, all outside the submitted work. No other conflict of interest is reported.

Legends to the figures

Figure 1

Flow chart of the participants of the 7th Tromsø Study

Figure 2

Venn-diagram showing associations between heart failure, COPD and mMRC ≥2 in 1538 participants

Figure 3

ROC curves showing predictive value of smoking, self-reported diseases, symptoms and signs + NT-proBNP for heart failure (HF), n= 1381, and chronic obstructive pulmonary disease (COPD), n=1370

Figure 4

Frequency of COPD[a] and 3 types of heart failure[b] by age in the 7th Tromsø Study

[a] COPD without concomitant HF, based on 7110 participants

[b] based on 1624 participants

Table 1 Characteristics of 1538 participants of the 7th Tromsø study by established diagnoses of heart failure and COPD.

	Heart failure, no COPD N=125		Heart failure and COPD N=14		COPD, no heart failure N=70		No COPD, no heart failure N=1329		All N=1538		p-value
	n	%	n	%	n	%	n	%	n	%	
Men	62	49.6	9	64.3	30	42.9	645	48.5	746	48.5	0.5
Women	63	50.4	5	35.7	40	57.1	684	51.5	792	51.5	
Age 40-59 years	12	9.6	2	14.3	19	27.1	437	32.9	470	30.6	<0.001
60-69 years	32	25.6	4	28.6	25	35.7	509	38.3	570	37.1	
70-84 years	81	64.8	8	57.1	26	37.1	383	28.8	498	32.4	
Smoking (15 missing)											
Never	47	38.2	0	0	7	10.0	537	40.8	591	38.8	<0.001
Previous	68	55.3	10	71.4	41	58.6	641	48,7	760	49.9	
Current	8	6.5	4	28.6	22	31.4	138	10.5	172	11.3	
Respiratory symptoms											
mMRC 0	0	0	0	0	16	22.9	1045	78.6	1061	69.0	<0.001
1	91	72.8	6	42.9	45	64.3	264	19.9	406	26.4	
2	21	16.8	7	50.0	5	7.1	15	1.1	48	3.1	
3-4	13	10.4	1	7.1	4	5.7	5	0.4	23	1.5	
Daily cough in periods of the year	27	21.6	7	50.0	31	44.3	199	15.0	264	17.2	<0.001
More short of breath than normal the examination day	20	16.0	3	21.4	19	27.1	111	8.4	153	9.9	<0.001
Crackles, wheezes (103 missing)											
Any crackle	23	20.0	3	23.1	15	22.1	162	13.1	203	14.1	0.03
Basal bilateral inspiratory crackles	6	5.2	1	7.7	4	5.9	21	1.7	32	2.2	0.007
Any wheeze	24	20.9	3	23.1	24	35.3	240	19.4	291	20.3	0.02
Ordinary or long expiratory wheezes	10	8.7	1	7.7	14	19.1	107	8.6	131	9.1	0.04
Self-reported diseases											
Myocardial infarction, (59 missing)	25	21.6	5	50.0	2	3.0	52	4.1	86	5.8	<0.001
Angina pectoris, (64 missing)	15	13.4	1	8.3	3	4.6	41	3.2	60	4.1	<0.001
Atrial fibrillation, (63 missing)	30	26.5	3	23.1	7	10.6	87	6.8	127	8.6	<0.001
Heart failure, (61 missing)	19	17.3	2	15.4	0	0	26	2.0	47	3.2	<0.001
Hypertension, (39 missing)	85	70.8	3	23.1	17	25.4	417	32.1	522	34.8	<0.001
Diabetes, (46 missing)	20	16.9	1	7.7	3	4.4	71	5.5	95	6.4	<0.001
COPD, (50 missing)	5	4.4	6	46.2	19	28.8	32	2.5	64	4.2	<0.001
Asthma, (45 missing)	16	13.9	5	38.5	28	41.2	126	9.7	175	11.7	<0.001
FEV_1 < LLN	12	9.6	9	64.3	33	47.1	60	4.5	114	7.4	<0.001
NT-proBNP >125 pg/ml	101	80.8	14	100	12	17.1	224	16.9	351	22.8	<0.001
NT-proBNP ≥ 97.5 percentile	41	32.8	4	28.6	1	1.4	44	3.3	90	5.9	<0.001
C-reactive protein ≥5 mg/L (9 missing)	13	10.5	2	14.3	8	11.4	83	6.3	106	6.9	0.08
SpO2 ≤ 95% (1 missing)	6	4.8	3	21.4	5	7.2	54	4.1	68	4.4	0.01

Table 2 Age adjusted Odds ratios for heart failure (n=139) and COPD (n=84) of clinical characteristics in 1538 participants. Missing values are shown in Table 1.

		Odds ratio (OR) for heart failure			Odds ratio (OR) for COPD		
		OR	95% CI	p-value	OR	95% CI	p-value
Male gender		1.1	0.8 – 1.5	0.7	0.9	0.6 – 1.4	0.7
Smoking	Never	ref			ref		
	Previous	1.2	0.8 – 1.7	0.4	5.7	2.6 – 12.7	<0.001
	Current	1.1	0.6 – 2.2	0.8	15.7	6.7 – 37.1	<0.001
Respiratory symptoms							
mMRC=0 -1		ref					
mMRC=2		21.6	11.2 – 41.7	<0.001	6.8	3.4 – 13.7	<0.001
mMRC 3-4		15.0	6.2 – 36.7	<0.001	5.3	1. – 15.0	0.002
Daily cough in periods		1.5	1.0 – 2.4	0.045	4.4	2.8 – 6.7	<0.001
More short of breath than normal the examination day		2.2	1.4 – 3.7	0.002	3.7	2.2 – 6.2	<0.001
Crackles							
Any crackles		1.2	0.7 – 1.9	0.5	1.7	1.0 – 3.0	0.06
Basal bilateral inspiratory crackles		2.2	0.9 - 5.2	0.09	3.0	1.1 - 8.1	0.03
Wheezes							
Any wheezes		1.0	0.6 – 1.5	0.9	2.0	1.3 – 3.3	0.004
Ordinary or long expiratory wheezes		0.8	0.4 – 1.6	0.6	2.2	1.2 – 4.0	0.01
Self-reported diseases							
Myocardial infarction ever		5.4	3.3 – 8.8	<0.001	2.0	0.9 – 4.2	0.08
Angina Pectoris ever		3.0	1.6 – 5.6	0.001	1.2	0.4 – 3.5	0.7
Atrial fibrillation ever		3.9	2.4 – 6.2	<0.001	1.5	0.8 – 3.0	0.3
Heart failure		7.7	4.1 – 14.4	<0.001	0.7	0.2 – 2.9	0.6
Hypertension ever		3.2	2.2 – 4.7	<0.001	0.6	0.3 – 0.9	0.03
Diabetes ever		2.7	1.6 – 4.7	0.005	0.7	0.3 – 2.0	0.5
COPD ever		1.9	1.0 – 3.9	0.06	16.7	9.3 – 29.9	<0.001
Asthma ever		1.7	1.0 – 2.8	0.06	6.3	3.9 – 10.1	<0.001
COPD detected		2.0	1.1 – 3.7	0.033			
Heart failure detected					1.9	1.0 – 3.6	0.039
FEV_1 <LLN		2.5	1.5 – 4.2	0.001	19.0	11.6 – 31,0	<0.001
NT-proBNP >125 pg/ml		21.0	12.7 – 34.6	<0.001	1.4	0.8 – 2.4	<0.001
NT-proBNP ≥ 97.5 percentile		11.2	6.9 – 18.1	<0.001	0.9	0.4 – 2.4	0.9
C-reactive protein ≥5 mg/L		1.5	0.8 – 2.7	0.2	1.8	0.9 – 3.6	0.09
SpO2 ≤ 95%		1.1	0.55 – 2.4	0.7	2.2	1.0 – 5.0	0.04

Table 3 Characteristics of 155 participants with heart failure in the 7th Tromsø study by type of heart failure

	HFrEF		HFmrEF		HFpEF		P-value
	n	%	n	%	n	%	
Men	37	61.7	16	48.5	22	35.5	0.02
Women	23	38.3	17	51.5	40	64.5	
Age 40-59 years	10	16.7	2	6.1	2	3.2	0.003
60-69 years	21	35.0	5	15.2	12	19.4	
70-84 years	29	48.3	26	78.8	48	77.4	
Smoking (2 missing)							
Never	20	26.7	12	36.4	21	35.0	0.6
Previous	47	62.7	19	57.6	31	51.7	
Current	8	10.7	2	6.1	8	13.3	
Respiratory symptoms							
mMRC							
1	41	68.3	16	48.5	47	75.8	0.1
2	14	23.3	10	30.3	7	11.3	
3-4	5	8.3	7	21.2	8	13.0	
Daily cough in periods of the year (7 missing)	17	28.3	8	25.8	10	17.5	0.4
More short of breath than normal the examination day	10	16.7	6	18.2	11	17.7	1.0
Crackles and wheezes (11 missing)							
Any crackle	12	21.1	6	20.0	13	22.8	0.9
Basal bilateral inspiratory crackles	3	5.3	2	6.7	4	7.0	0.9
Any wheezes	16	28.1	3	10.0	14	24.6	0.2
Ordinary or long expiratory wheezes	6	10.5	2	6.7	6	10.5	0.8
Self-reported diseases							
Myocardial infarction, (11 missing)	13	22.8	9	30.0	14	24.6	0.8
Angina pectoris, (15 missing)	7	13.0	5	17.9	7	12.1	0.8
Atrial fibrillation, (15 missing)	15	27.8	11	39.3	12	20.7	0.2
Heart failure, (18 missing)	11	20.0	7	25.9	4	7.3	0.057
Hypertension, (9 missing)	32	57.1	24	77.4	39	66.1	0.2
Diabetes, (8 missing)	13	22.8	6	20.7	3	4.9	0.015
COPD, (12 missing)	5	8.9	3	10.3	9	15.5	0.5
Asthma, (12 missing)	9	16.1	6	20.7	13	22.4	0.7
FEV_1 < LLN (10 missing)	14	23.7	4	12.9	8	14.5	0.3
COPD, defined by spirometry and symptoms (16 missing)	6	10.3	2	6.9	6	11.5	0.8
NT-proBNP >125 pg/ml	35	58.3	33	100	62	100	<0.001
NT-proBNP ≥ 97.5 percentile	18	30.0	17	51.5	16	25.8	0.03
C-reactive protein ≥5 mg/L (1 missing)	8	13.6	5	15.2	4	6.5	0.3
SpO2 ≤ 95%	4	6.7	1	3.0	7	11.3	0.3

Appendix

97.5 percentile of NT-proBNP by age based on 1981 blood donors aged 18-65 years and 283 patients aged between 50 and 90 years without symptoms or history indicating increased risk of heart disease, table found in an Instructions for use from Roche Diagnostics, Norway.

Age (years)	**Women**	**Men**
18-44	130 pg/ml	86 pg/ml
45-54	249 pg/ml	121 pg/ml
55-64	287 pg/ml	210 pg/ml
65-74	301 pg/ml	376 pg/ml
≥75	738 pg/ml	486 pg/ml

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Figure 1

Click here to access/download;Figure;Figure 1 (Flow diagram).tif

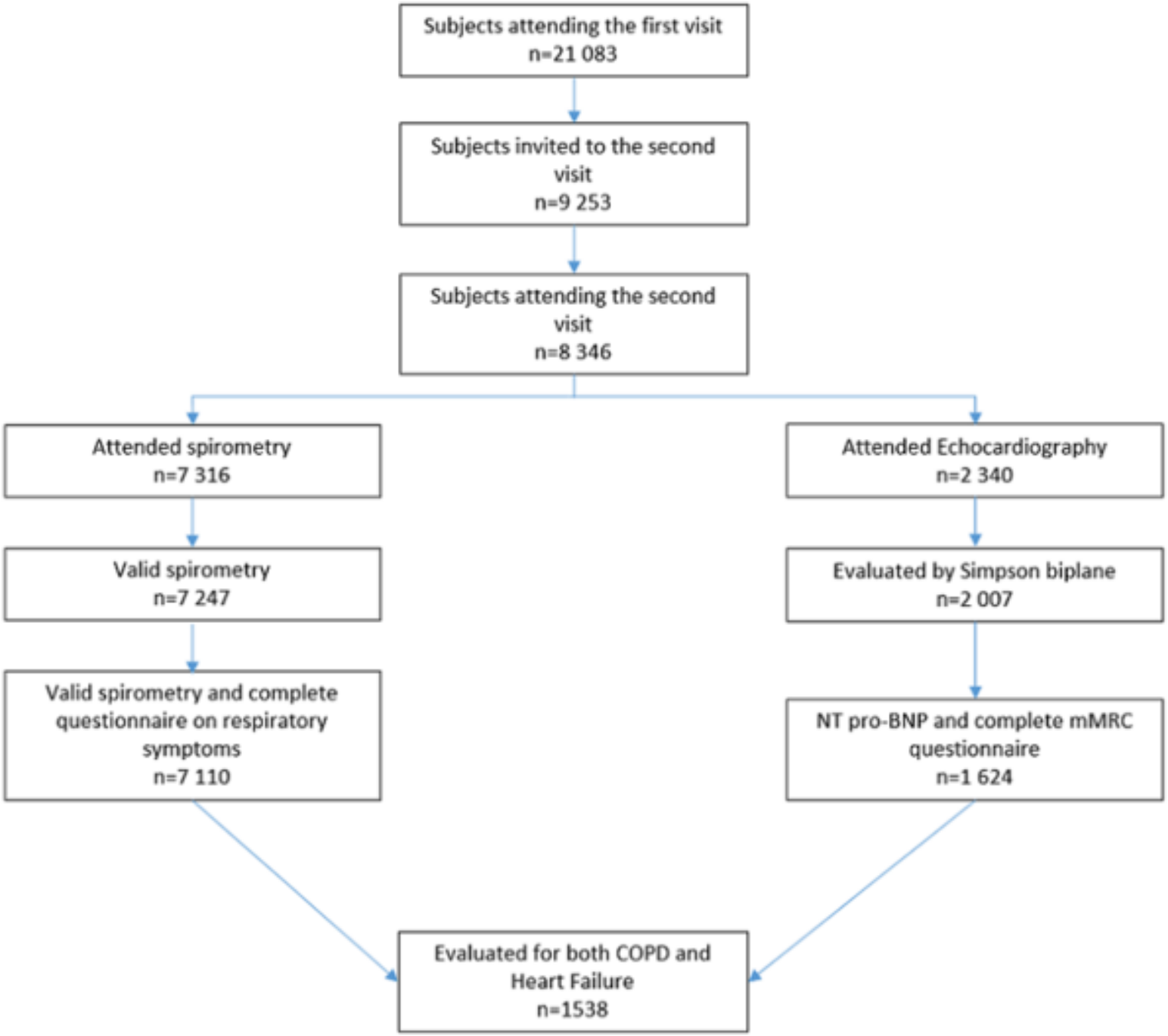


Figure 2

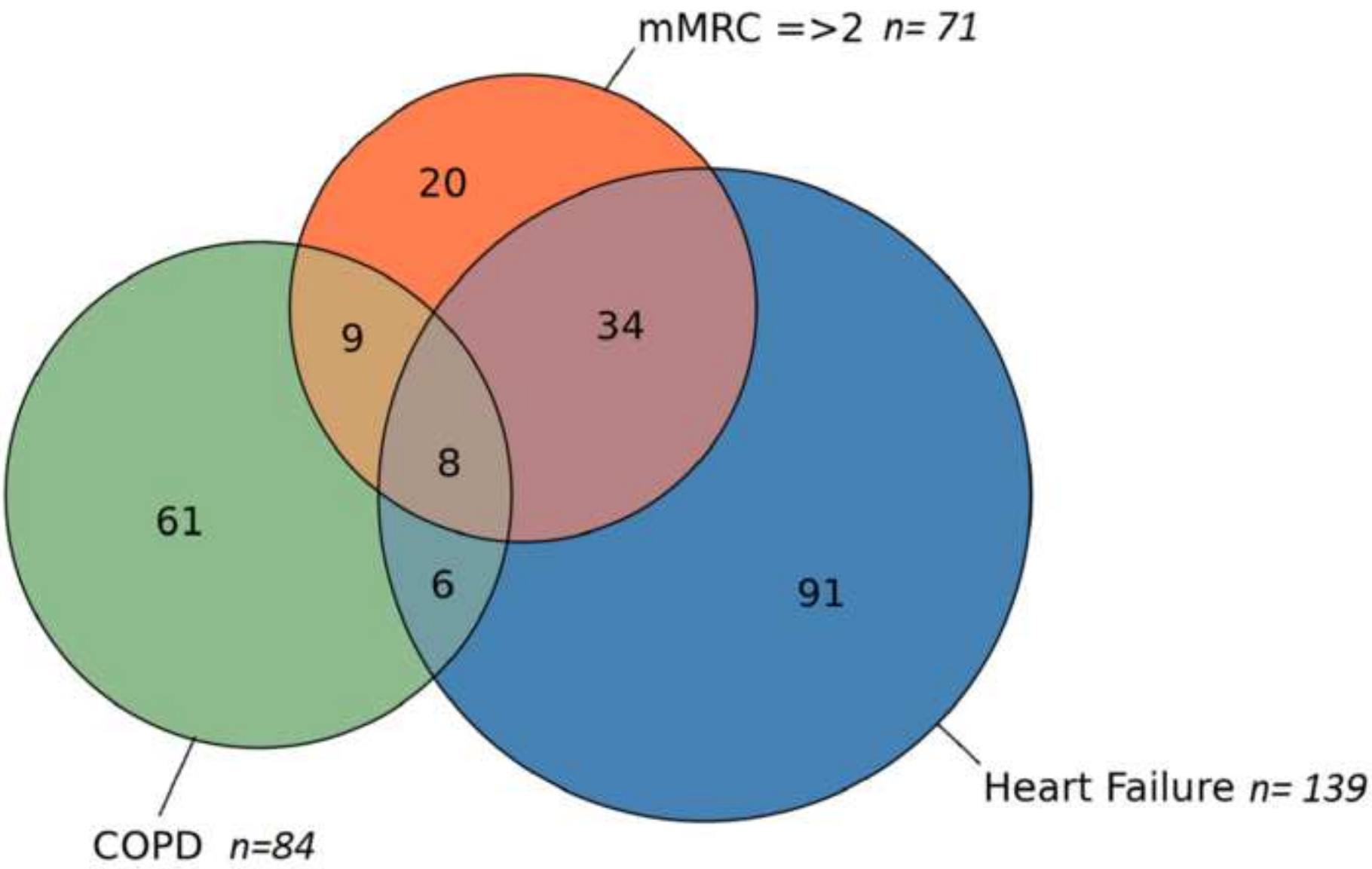
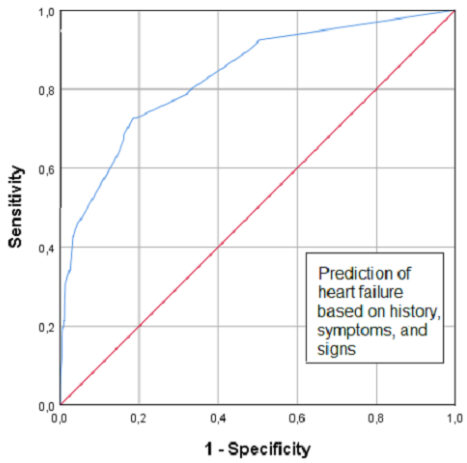
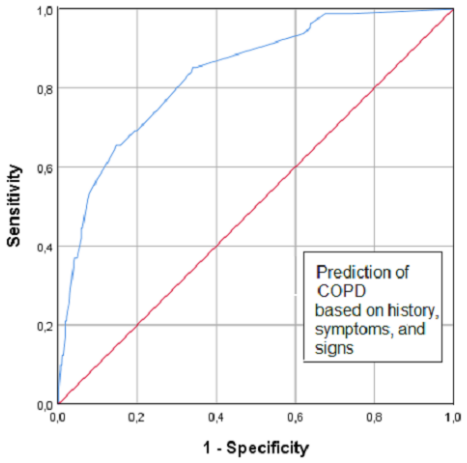


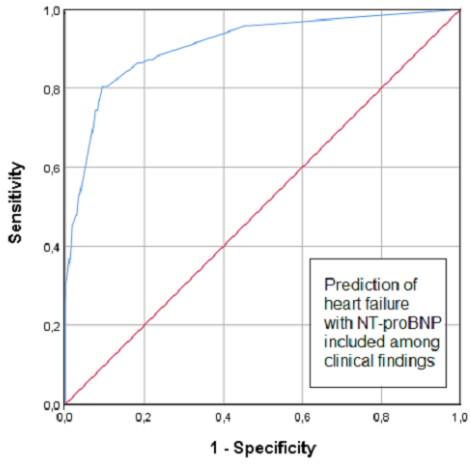
Figure 3



AUC 0.833 (95% CI 0.790 - 0.875)
Score:
Age ≥70 * 1.433 + Myocardial infarction * 0.951 + Hypertension * 1,141
+ Atrial fibrillation * 1.130 + mMRC ≥2* 2.905 + basal insp. crackles * 1.296



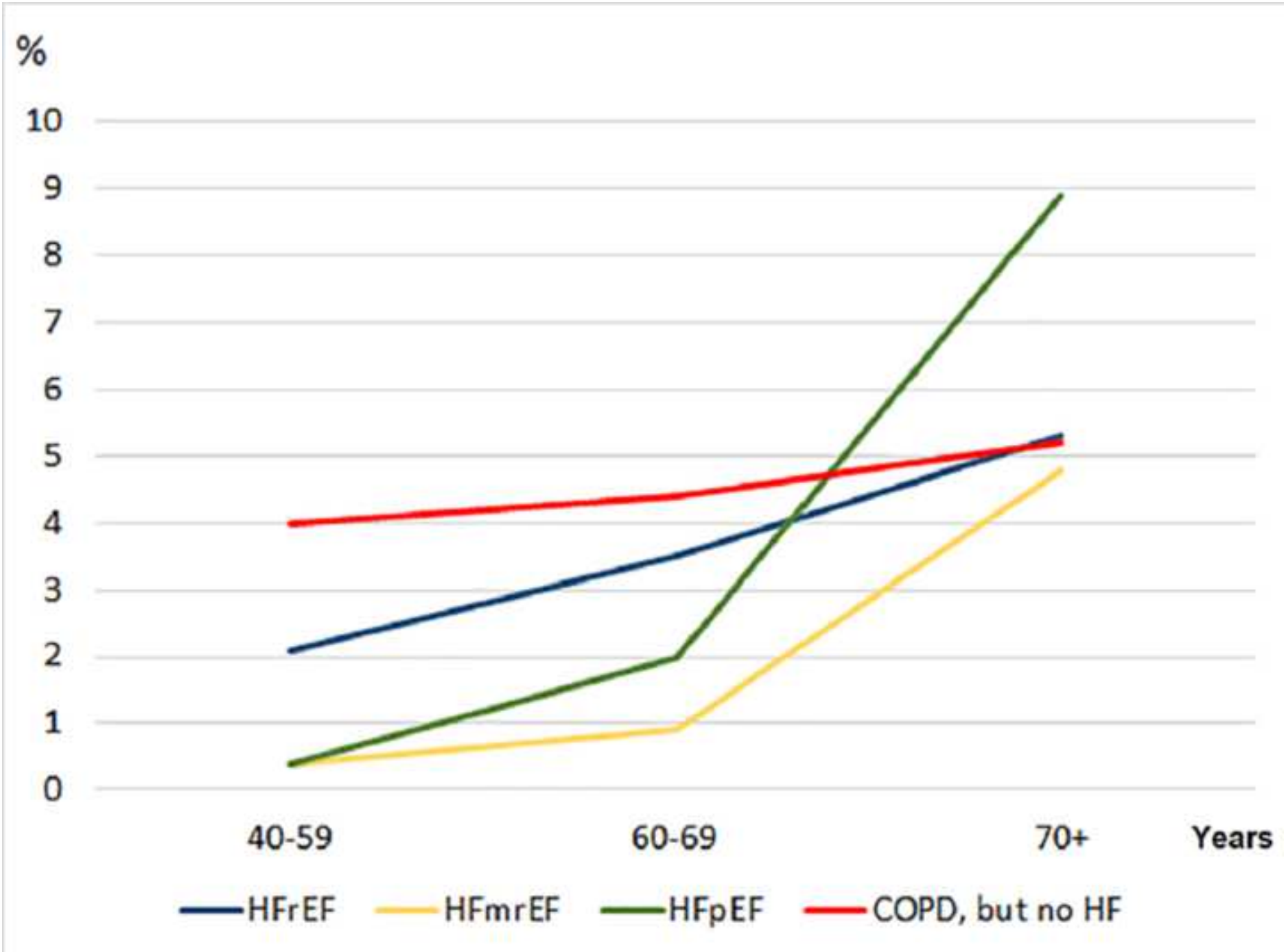
AUC 0.829 (95% CI 0.783 - 0.875)
Score:
Current smoker * 2.335 + Former smoker * 1.508 + Cough daily in periods * 0.967
+ mMRC ≥2 * 0.996 + Increased dyspnoea examination day * 0.636
+ Asthma * 1.369 + Any wheeze * 0.636



AUC 0.909 (95% CI 0.877 - 0.940)
Score:
Myocardial infarction * 0.641 +
Hypertension * 1.259 +
Atrial fibrillation * 0.666 +
mMRC ≥2* 3.141 +
NT-proBNP >125 pg/ml and NT-proBNP <97.5 percentile * 2.885 +
NT-proBNP ≥ 97.5 percentile * 3.240

Figure 4

Click here to access/download;Figure;Figure 4.tif



Appendix

Links to the Tromsø Study invitation letters, questionnaires and informed consent forms

Tromsø 4:

Invitation: http://uit.no/Content/271754/T4_Invitation.pdf

Questionnaire 1: http://uit.no/Content/271764/T4_Q1.pdf

Invitation phase 2: http://uit.no/Content/271753/T4_Information_brochure_Phase2.pdf

Questionnaire 2:

- Less than 70 years of age: http://uit.no/Content/430574/T4_Q2_U70.pdf

- 70 years of age or more: http://uit.no/Content/271765/T4_Q2_O70.pdf

Consent form: http://uit.no/Content/70750/samtykkerklaeringer-pdf

Tromsø 5:

Invitation: http://uit.no/Content/271757/T5_Invitation.pdf

Questionnaire 1:

- Less than 70 years of age: http://uit.no/Content/430584/T5_Q1_U70.pdf

- 70 years of age or more: http://uit.no/Content/430586/T5_Q1_O70.pdf

Invitation phase 2: http://uit.no/Content/271756/T5_Information_brochure_Phase2.pdf

Questionnaire 2: http://uit.no/Content/430588/T5_Q2.pdf

Consent form: http://uit.no/Content/70750/samtykkerklaeringer-pdf

Tromsø 6:

Information brochure: http://uit.no/Content/100340/Forespoersel_om_deltakelse_t6.pdf

(In Norwegian only)

Questionnaire 1: http://uit.no/Content/401052/Questionnaire_T6_1.pdf

Questionnaire 2: https://uit.no/Content/100351/Spoerreskjema_2_t6.pdf

Consent form: http://uit.no/Content/111929/samtykke%20Tr6.pdf

Tromsø 7:

Information brochure: https://uit.no/Content/467891/brosjyre.troms%C3%B87.pdf
(In Norwegian only)

Questionnaire 1: https://uit.no/Content/507611/Q1%20Troms%C3%B8%207.pdf

Questionnaire 2: https://uit.no/Content/507612/Q2%20Troms%C3%B87.pdf

Consent form:
https://uit.no/Content/575211/cache=20180805144729/Samtykke.den7.Tromsoundersokelsen.pdf