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Prevalence and cause of Dyspnea in a general population: The Tromsø Study

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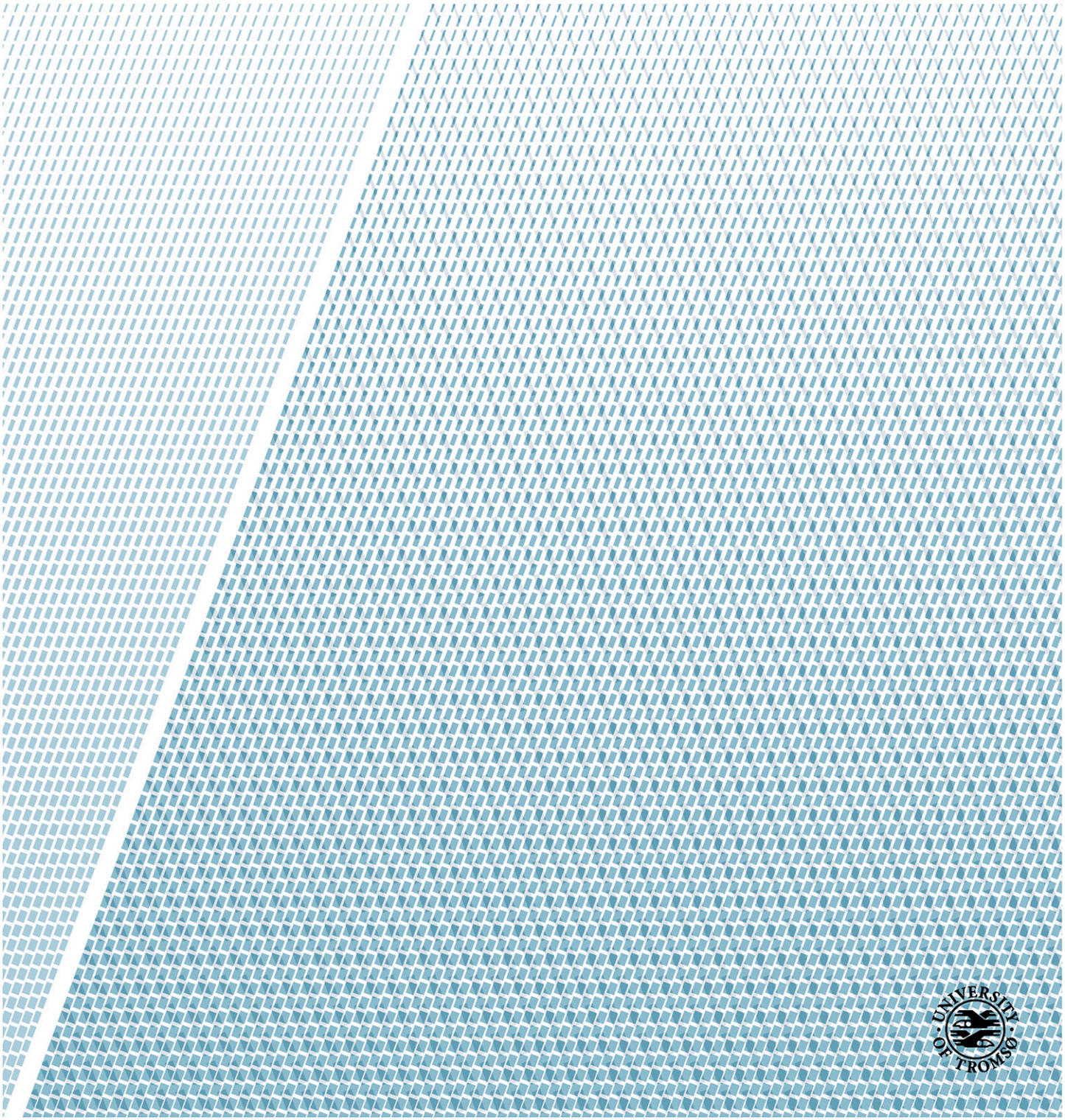

PREFACE

This dissertation is original, unpublished, independent work submitted for the degree of Master in Public Health at The Artic University of Norway. The described project Prevalence and cause of dyspnea in general population was conducted under the supervision of Professor Henrik Schirmer in the Department of Clinical Medicine and co-supervision of Professor Hasse Melbye in the General Practice Research Unit.

This work is to the best of my knowledge original, except where literature review and references are made to previous work. This dissertation has not been or is being submitted to any other degree or qualification at any other university.

I would like to express my sincere gratitude to my supervisor and co-supervisor for their continuous supervision, advices, feedback and guidelines. This project would never have been done without their expertise and support. Also, I am very grateful to Department of community medicine, The Artic University of Norway for equipping me with valuable learning tools and warm support during my study period.

Finally, I would like to thank my family and my friend Sanjit Jung Thapa for their moral support and constant believing in me.

ABSTRACT

Background: Dyspnea is a prevalent condition causing reduced quality of life increasingly by age. The main causes are heart failure (HF), chronic obstructive pulmonary disease (COPD) with less common conditions being ischemic dyspnea, heart disease, atrial fibrillation, asthma, and pulmonary fibrosis. The aim of study was to determine causes of dyspnea in a general population through examination with echocardiography and spirometry and determine age and gender specific prevalence of each condition.

Methods: This population based cross-sectional study included 11812 (46.9% were men) participants with answered questionnaire data on dyspnea from the sixth survey of Tromsø study. Independent-sample *T*-test (for continuous variables) and Chi-square test (for categorical variables) were used to explore significant difference in participant´s characteristics between men and women. Differences between groups were compared with ANOVA for continuous variable and logistic regression (univariate / multivariable analysis) was performed with dyspnea along demographic and baseline characteristics, COPD, restrictive disease and spirometry and echocardiography measurement group.

Results: Overall 48.6% of the total participants reported dyspnea. Among participants with moderate COPD prevalence of dyspnea was 67.3% for men and 75% for women. The prevalence of enlarged LAD/BSA increased from 15% in subjects without self-reported dyspnea to 30% in moderate dyspnea without further increase with increasing severity. Only 25.2% of the participants reporting dyspnea symptoms had abnormal measurements. Among them only 43.6% of male subjects reporting dyspneic symptoms had abnormal measurements compared to 56.4% of women reporting dyspneic symptoms. Increase in severity of COPD was associated with increased prevalence of dyspnea. Moderate COPD [OR=2.6; 95% CI: 1.5-4.5] and severe COPD [OR=9.4; 95% CI: 2.0-44.7] were significantly associated with increased prevalence of dyspnea.

Conclusion: Our study shows a strong association between self-reported dyspnea and diastolic heart failure, restrictive pulmonary disease and increasing levels of COPD.

Keywords: *Dyspnea, heart failure, COPD, Prevalence, echocardiography, spirometry*

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LIST OF ABBREVIATIONS

AFib	Atrial Fibrillation
ANOVA	Analysis of Variance
BMI	Body Mass Index
BSA	Body Surface Area
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DBP	Diastolic Blood Pressure
DHF	Diastolic Heart Failure
FEV_1	Forced Expiratory Volume in One Second
FEV_3	Forced Expiratory Volume in Three Second
FEV_6	Forced Expiratory Volume in Six Second
FVC	Forced Vital Capacity
LA	Left atrial
LAD/BSA	Left Atrium Index by Body Surface Area
LV	Left Ventricular
MRC	Medical Research Council
OR	Odd Ratio
PEF	Peak Expiratory Flow
SBP	Systolic Blood Pressure
SD	Standard Deviation
Sao_2	Oxygen Saturation
SPSS	Statistical Package for the Social sciences
USA	United State of America

WHO	World Health Organization

1.BACKGROUND

Dyspnea is a prevalent condition causing reduced quality of life increasingly by age and is a common problem affecting up to half of patients admitted to acute, tertiary care hospitals (1) and one quarter of ambulatory patients (2, 3). Clinicians use the term dyspnea, while patients rather describe it with terms such as breathlessness, shortness of breath, chest tightness, and air hunger or as increased effort of breathing (4). These different terms indicate that defining dyspnea (5) is complex and will vary between patients. Extensive research has been done on the pathophysiological aspects of dyspnea, but to date, the precise physical mechanism of breathlessness is unclear (6). And, although the affective contribution to a perception of breathlessness has been examined, the nature of its contribution to dyspnea has been difficult to find (6). When dyspnea occurs at rest or during mild to moderate exertion, it is considered pathologic and a symptom of disease state (7). The presence of dyspnea predicts long-term mortality (8) and characterizes high-prevalence diseases like congestive heart failure (CHF), ischemic heart disease, chronic obstructive pulmonary disease (COPD), and asthma. There are numerous causes of dyspnea although patients diagnosed within respiratory and cardiovascular disease account for approximately two-third of all cases (9). The prevalence of dyspnea has varied greatly across studies and countries (10-12). The variation might be due to differences in the distribution of known correlates of dyspnea such as age, sex and smoking status (10, 12, 13). But differences might also reflect variation in how dyspnea was measured; the nature of the samples studied and the burden of chronic disease that cause dyspnea. Dyspnea is extremely common with advancing disease, and at late stages is present in 90-95% of those with COPD, 60-80% of those with CHF and 10-70% of those with cancer, whilst also being common in end-stage kidney disease and most severe in primary lung cancers, affecting 90% (14). Prevalence of dyspnea varies among clinical settings and patient subgroups; in the community 3% to 25%, outpatient clinics 3.7%, emergency rooms 2.7%, and at hospital admissions 15% to 25% (15). Population-based studies have shown a prevalence of 9 to 13% for mild to moderate dyspnea among community-residing adults (8, 16, 17), 15

to 18% among community-residing adults aged 40 years or older (16, 18, 19), and 25 to 37% of adults aged 70 years and older (20). Other population-based studies have reported an overall dyspnea prevalence of more than 20% (2, 10, 12, 21). A high- prevalence of cardiopulmonary disease, life-style changes, obesity and subclinical medical conditions might have explained this dyspnea. Several other factors associated with increased prevalence include older age, obesity, smoking, low socio-economic status and female gender (15). About 60% of those presenting with dyspnea are aged 65 years or more (22). However, dyspnea remains difficult to evaluate, especially in an elderly population, because of its subjective nature and the small margin between disease and physical deconditioning due to ageing (23). Therefore, the reported prevalence of dyspnea in the community seems to vary widely ranging from 20 to 60% in elderly populations (15). Cardiac and pulmonary etiology was most frequent, usually in the form of congestive heart failure, asthma or chronic obstructive lung disease (15). More attention to dyspnea, including its early detection, may be important for a variety of reasons: dyspnea is a common complaint (24-26) with a marked negative influence on daily functioning and quality of life (5, 26), acute or severe dyspnea requires prompt and adequate pharmacological intervention (27) and it is an important contributor to mortality (5, 25). Early evaluation of dyspnea can have a positive influence on the patient's functional condition, thus promoting and prolonging an active and independent lifestyle (28). Hence, the prevalence and limits to exertion caused by dyspnea needs to be defined across the whole population irrespective of health service utilization (17).

1.1 Congestive heart failure

With increasing life expectancy, heart failure has become an increasing health problem in industrialized countries (29). Heart failure was earlier understood as pump failure or left ventricular (LV) systolic dysfunction, but several studies found that several patients admitted with heart failure had normal systolic function (30-32) and were labeled as heart failure patients with normal LV systolic function, later on defined as separate entity as Diastolic heart failure (DHF) (33). This group consisted of elderly, obese and hypertensive patients (33), mostly with delayed left ventricular relaxation and

also some with decreased left ventricular compliance and consequently reduced filling dynamics and increased left ventricular end-diastolic pressure (34). In earlier studies DHF was presumed to account approximately one-third of all patients with heart failure (35) but over the last two decades, these perspective have changed substantially with an increase in the prevalence of DHF from 38% to 54% of all heart failure cases (35). Patients with acute dyspnea are present in emergency departments and intensive care units every day. Acute dyspnea is mostly due to potentially life-threatening cardiac or respiratory conditions, and treating it promptly requires understanding of the underlining mechanism (36). Patients with heart failure are frequently limited in their activities of daily living by exertion dyspnea. One hypothesis for dyspnea is that the reduced cardiac output that occurs during exercise in patients with heart failure results in respiratory muscle ischemia and ultimately, respiratory muscle fatigue (37). Depending on the hospital setting, acute heart failure accounts for 30% to 70% of acute dyspnea in the emergency departments (36). Quick identification of acute heart failure remains crucial and lifesaving, and may lead to prompt admission of the patients in a specialized cardiovascular intensive care unit. A simple and quick way of differentiating cardiac and pulmonary causes of dyspnea is essential in patients admitted to the emergency departments and should be based on routine procedure. In practice, medical history, symptoms, physical examination, chest x-ray, electrocardiogram and, more recently, blood B-type natriuretic peptide values are useful tools for detecting acute heart failure in patients presenting with acute dyspnea (36). Heart failure is then confirmed by echocardiography.

1.2 Coronary heart disease (CHD)

The prevalence of coronary heart disease (CHD) increases with increasing age. However, in many developed countries, CHD mortality has decreased during the last two decades (38). Symptomatic presentation of CHD varies widely. Individuals with CHD present both with and without symptoms (39). Dyspnea may be the only symptom of CHD but may also precede angina pectoris as a manifestation of CHD in 10-15% of referred cases (40). For symptomatic patients, dyspnea has been considered as an angina equivalent on the basis of increased prevalence and severity of myocardial

ischemia and heightened mortality risk compared to asymptomatic patients or symptomatic patients with non-cardiac or atypical angina (39). Recently, the prognostic relationship between dyspnea and CHD in individuals undergoing non-invasive CHD testing has been observed, although the pathophysiologic mechanism that underline adverse prognosis as a function of dyspnea has been to date poorly understood (39). The potential mechanisms explaining the relationship of dyspnea to obstructive CHD have been little examined (39). In a series of elegant experiments, Pepine et al. (41) demonstrated that myocardial ischemia-induced left ventricular dysfunction perpetuates increased left ventricular end-diastolic pressure, which in turn increases lung airway resistance and reduced lung compliance and thereby causes dyspnea.

1.3 Chronic obstructive pulmonary disease (COPD)

As COPD progresses, many individuals experience frequent acute exacerbations of incapacitating dyspnea requiring emergency admission to hospital (6). Dyspnea is one of the most common symptoms in chronic obstructive lung disease and it is invariably present in all severity stages either at rest or under conditions of exercise (42). Breathing difficulty is the major reason that patients with COPD seek medical attention. A variety of studies have demonstrated that patients with different respiratory disease report unique descriptors of their dyspnea (43). In particular, patient with COPD describe their breathlessness as related to the work and effort associated with breathing (43). In addition, patients with COPD responded that their breathing difficulty was perceived more frequently during inspiration rather than during expiration (4). Despite the wide range of available treatment, as many as 50% (42) of all patients with COPD presents with shortness of breath. In a study Rennard et al. (44) reported that more than 50% of respondents to a telephone survey with COPD reported that dyspnea limited sports and recreation activities as well as normal physical exertion and about 40% indicated that their breathing affected their ability to perform household chores. Several cross-sectional studies have reported the a prevalence of dyspnea in population samples of respondent's self-reporting diagnosis of COPD, chronic bronchitis or with airflow limitation identified using spirometry screening (45). However, there is limited information about the occurrence, distribution and outcomes associated

with dyspnea among patients with diagnosed COPD who are managed in primary care (45). A cross-sectional study of COPD patients selected from primary care offices in several European countries reported an 80% prevalence of dyspnea (46). However, these data are from a selective group of patients and it was not possible to show an association with prospectively evaluated outcomes (46).

2. RATIONALE OF THE STUDY

Dyspnea is a very common symptom and persistent shortness of breath can interfere greatly with quality of life (23). Dyspnea is a key target in both clinical management and clinical trials of acute heart failure syndrome and lung disease and its relief important to patients, clinicians, investigators, and regulatory approval agencies (17). Despite its importance, the impact of early therapy on dyspnea is not well known. Extensive research has been done on the pathophysiological aspects of dyspnea, but to date, the precise physical mechanism of breathlessness is unclear (17). And, although the affective contribution to a perception of breathlessness has been examined, the nature of its contribution to dyspnea has been difficult to find. Therefore, accurate diagnosis and a greater awareness and understanding of modulating factor can facilitate targeted treatment of dyspnea and subsequently dramatically improve clinical conditions (15).

3. PURPOSE OF THE STUDY

3.1 General objective

To explore the prevalence and causes of dyspnea in a general population

3.2 Specific objectives

a) To explore whether dyspnea differ in general characteristic from those not reporting dyspnea.

b) To assess to what extent the dyspnea is related to cardiac or respiratory measures of disease.

4. MATERIALS AND METHODS

4.1 Study design

Population based cross sectional study

4.2 Study area

The Tromsø study consists of six surveys (referred to as Tromsø 1-6) that have been conducted in the municipality of Tromsø from 1974 to 2008. The Tromsø study population includes subjects who have attended at least one of the six surveys. The sixth survey of the Tromsø study (Tromsø 6) was used for this study.

4.3 Study population and Study period

The study population consisted of all men and women aged 30-87 from the sixth survey of the Tromsø study (Tromsø 6). It was conducted in 2007-08. During the Tromsø 6 study, a total of 12984 men and women aged 30-87 took part. Finally, after excluding all the non-eligible participants with missing questionnaire data on dyspnea 11812 participants were included. Within this group, 1764 Subjects had both been examined by spirometry and echocardiography enabling estimation of prevalence of signs of cardiac and pulmonary disease among those reporting dyspnea.

4.4 Data collection

The residents of the municipality of Tromsø were invited to take part in the survey based on the official population registry. Data in Tromsø 6 study were collected in two visits. A personal invitation was mailed and subjects were free to attend whenever suitable. Information about the survey and the examination was included in the invitation leaflet. Non-attendees were given one reminder. Participants eligible for the second-visit examinations were identified before they were to attend the first visit of the survey and were invited to the second-visit examination 2-4 weeks after the completion of first visit.

4.5 Study variables

a) Dyspnea

The participants were asked about their perceived breathlessness and were then classified into MRC dyspnea grades, according to how they perceived their disability (47).

No dyspnea: Patient-complaining no breathlessness.

Mild dyspnea: Patient-complaining discomfort in breathing with ordinary physical activities i.e. discomfort when walking rapidly on level ground or up a moderate slope.

Moderate dyspnea: Patient-complaining discomfort in breathing after walking 100 yards or after a few minutes on the level.

Severe dyspnea: Patient-complaining discomfort in breathing with less than ordinary physical activities i.e. walking calmly on level ground or washing and dressing.

Very severe dyspnea: Patient- complaining discomfort in breathing at rest.

b) Spirometry

The participant's lungs function was measured by spirometry. The following measurements were normalized according to gender, age and height.

FEV1, FVC and FEV1/FVC. To ensure quality of measurements following measurement was also included: FEC, FEV75%, PEF, FEV_3 and FEV_6.

Predicted FEV1 and FVC were calculated using the formula (48):

Predicted FEV1

*Men: exp (-10.556+2.342*Ln (height)-0.0000685*age*age)*

*Women: exp (-9.091+2.004*Ln (height)-0.000163*age*age+0.007237* age)*

Predicted FVC

*Men: exp (-12.396+2.733*Ln (height)-0.0000592*age*age)*

*Women: exp (-9.851+2.189*Ln (height)-0.000163*age*age+0.007237*age)*

Thereafter, % predicted FEV1 and FVC for men and women was calculated as,

*[Measured (FEV1)/Predicted (FEV1)]*100 and [measured (FVC)/Predicted (FVC)]*100 respectively.*

Spirometer (with obstructive pattern) was indicated normal if FEV1/FVC ≥ 0.7 and FEV1 ≥ 80% or FVC ≥ 80% predicted and was indicated abnormal if FEV1/FVC < 0.7 was recorded.

c) Chronic Obstructive Pulmonary disease (COPD)

Patients with COPD will be categorized in different stages of COPD based upon spirometric definition of COPD according to GOLD criteria (42).

Stage 1. Mild	FEV_1/FVC <0.7 FEV_1 ≥ 80% predicted With or without symptoms
Stage 2. Moderate	FEV_1/FVC <0.7 50% ≤ FEV_1 <80% predicted With or without symptoms
Stage 3. Severe	FEV_1/FVC <0.7 30% ≤ FEV_1 <50% predicted With or without symptoms
Stage 4. Very Severe	FEV_1/FVC <0.7 FEV_1< 30% predicted or FEV_1 <50% predicted plus chronic Respiratory failure

d) Echocardiography

The participants left atrium size were measured by parasternal short axis recording of M-mode through aortic root and left atrium. Reference limits for left atrial dimensions was categorized as normal if LA diameter/ BSA (cm/m^2) was <2.3 and abnormal if LA diameter/BSA (cm/m^2) was ≥ 2.3. Patients with Left atrial diameter index to BSA > 2.3 cm/m^2 was used as an indicator of increased end diastolic pressure due to diastolic dysfunction of varying reason (35).

e) Independent variables

Baseline demographic characteristics: *age, sex, measurements, self-reported disease, smoking, alcohol, exercise and education*.

Age was divided into 6 groups: 30-3, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years. Measurements such as systolic blood pressure, diastolic blood pressure, body mass index, oxygen saturation (Sao_2), cholesterol, glucose and heart rate was recorded. For systolic and diastolic blood pressure measurement 3 reading was recorded and the mean of reading 2 and 3 was used in the analysis. Body mass index was categorized according to WHO criteria as normal, overweight and obese if BMI<25kg/m^2, BMI 25-2925kg/m^2 and BMI≥ 30kg/m^2 respectively (49). The participants reported any presence of diabetes, heart attack, atrial fibrillation, angina, asthma and bronchitis were included as self-reported disease. Smoking habits were reported as: never, former or current smokers. Similarly, alcohol intake of participants was categorized as: never, monthly or weekly. The participants exercise level was recorded and categorized into three groups: easy, (you do not become short-winded or sweaty) moderate (you become short-winded or sweaty) and hard exercise level (you become exhausted). The participants' educational level was categorized into five groups: Primary/secondary school or modern secondary school, Technical school/vocational school/1-2 years senior high school, High school diploma, College/university less than 4 years and College/university 4 years or more.

4.6 Data analysis

Data analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL. USA). Presence of normalcy was evaluated for each continuous variable. Independent-sample *T*-test (for continuous variables) and Chi-square test (for categorical variables) were used to explore significant difference in participant´s characteristics between men and women. All the demographic and baseline characteristics were used as independent variables in the analysis. Differences between groups were compared with ANOVA for continuous variable adjusting for age. Furthermore, a dichotomous variable dyspnea (present/absence) was made and logistic regression (univariate / multivariable

analysis) was performed with dyspnea along demographic and baseline characteristics, COPD, restrictive disease and spirometer and echocardiography measurement group to explore the significant association between them. The graphical method was used, where the bar graph indicates the age distribution of prevalence of dyspnea between men and women.

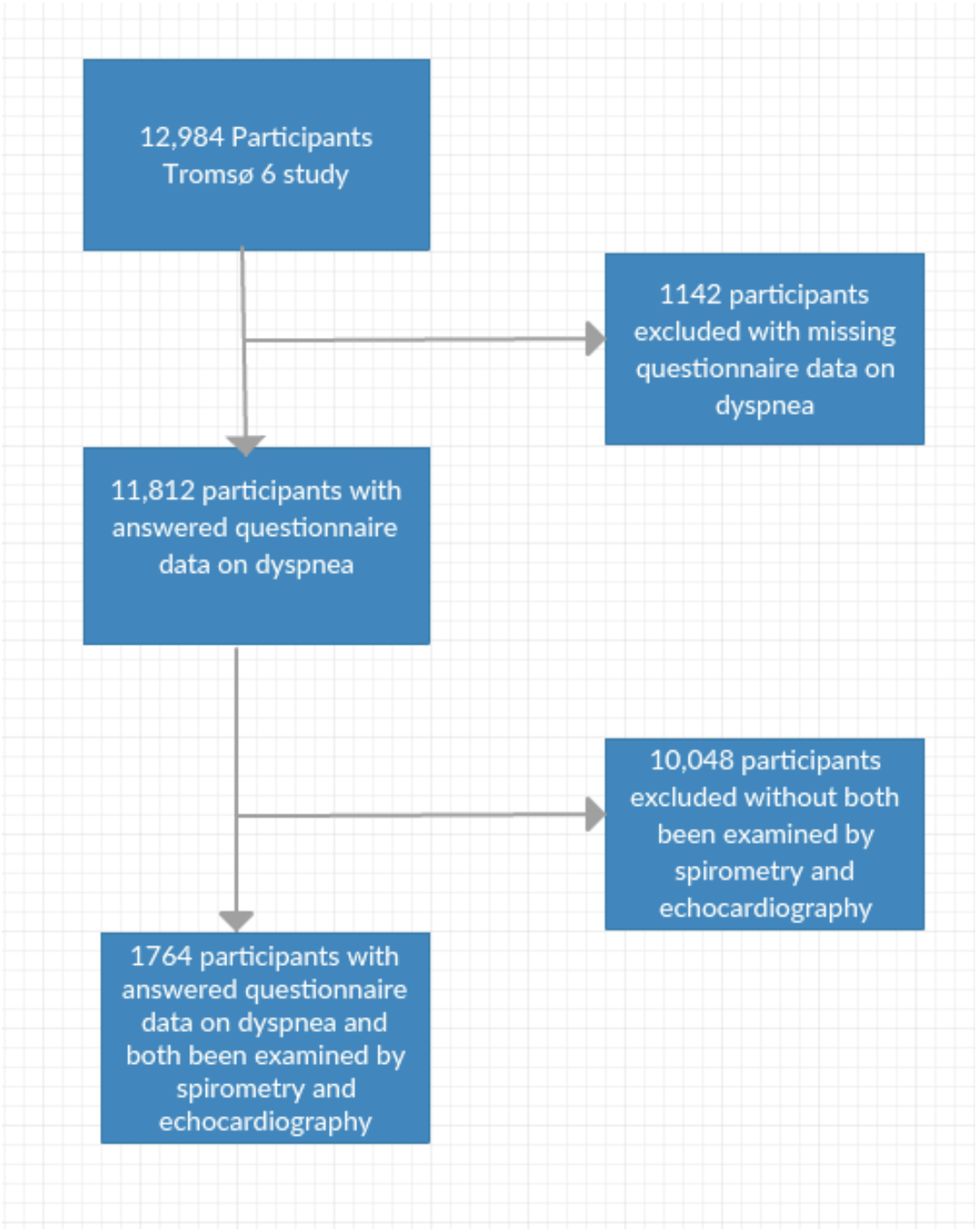

Figure 1: Profile of the study population used in analysis

5. ETHICAL CONSIDERATION

The Regional Committee on Research Ethics North Norway approved this project for the Tromsø 6 Survey.

6. RESULTS

Demographic and baseline characteristics

The baseline and demographic characteristics of men and women are summarized in Table 1. Men constitute 46.9% of the total sample and the mean age was 57.2 years for men and 57.4 years for women. The mean systolic and diastolic blood pressure was 137.7 and 81.1 mmHg for men and 133.4 and 74.8 mmHg for women (p value <0.001). The mean body mass index was 27.2 kg/m^2 for men and 26.5 kg/m^2 for women (p value <0.001) .The proportion of Obesity was 20.3 % among men and 20% among women and proportion of overweight was 51.6% among men and 38.3% among women. Mean oxygen saturation (SaO_2) was 97.1 for men 97.5 for women (p value <0.001). Mean total serum cholesterol level was 5.5mmol/l for men and 5.6mmol/l for women (p value <0.001), while the mean glucose level was 5.7mmol/l for men and 5.3mmol/l for women (p value <0.001). Among the self-reported diseases, asthma (8.6%) and heart attack (8.2%) was more prevalent among men and asthma (11%) was more prevalent among women. Overall 46.8% of the total participants reported dyspnea. Among men who reported dyspnea 38.9%, 1.3%, 2.5% and 1.4% had mild, moderate, severe and very severe dyspnea respectively compared to 42.3%, 1.7%, 2.8% and 2.5% of women with self-reported dyspnea. A significantly higher proportion of men compared to women reported former or current daily smoking. Alcohol intake was higher among men compared to women. Men were more physically active than women. Men had higher educational level than women especially regarding technical or vocational school and lower degree university school (less than 4 years).

Table 1: Demographic and baseline characteristic of men and women in the study population

Characteristics	Total	Men	Women	P value
Valid n (%)	11812	5537 (46.9)	6275 (53.1)	
Age in years (SD)	57 (12.6)	57.4(12.2)	57.2(12.9)	< 0.001
Measurements				
Mean SBP (SD)	135.4 (22.9)	137.7 (20.3)	133.4 (24.8)	< 0.001
Mean DBP (SD)	77.7 (10.6)	81.1 (10.1)	74.8 (10.2)	< 0.001
BMI kg/m^2 (SD)	26.9 (4.2)	27.2 (3.8)	26.5 (4.7)	< 0.001
BMI kg/m^2 category				< 0.001
BMI<25 n (%)	4264 (35.3)	1556 (28.1)	2608 (41.6)	
BMI 25-29 n (%)	5255 (44.5)	2853 (51.6)	2402 (38.3)	
BMI ≥ 30 n (%)	2380 (20.2)	1125 (20.3)	1255 (20)	
SaO_2 (SD)	97.3 (2.1)	97.1(2.1)	97.5 (2.1)	< 0.001
Cholesterol (SD)	5.6 (1)	5.5 (1)	5.6 (1.1)	< 0.001
Glucose (SD)	5.5 (1.5)	5.7 (1.6)	5.3 (1.3)	< 0.001
Heart rate (SD)	65.5 (10.7)	64.5 (11)	66.4 (10.3)	< 0.001
Self-reported disease				
Diabetes n (%)	557 (4.8)	296 (5.5)	261 (4.3)	0.003
Heart attack n (%)	616 (5.3)	447 (8.2)	169 (2.8)	< 0.001
AFib n (%)	658 (5.8)	352 (6.6)	306 (5.1)	0.001
Angina n (%)	552 (4.8)	329 (6.1)	223 (3.6)	< 0.001
Asthma n (%)	1136 (9.8)	463 (8.6)	673 (11)	< 0.001
Bronchitis n (%)	503 (4.4)	226 (4.2)	277 (4.5)	0.3
Level of self-reported Dyspnea				< 0.001
No n (%)	6284 (53.2)	3092 (55.8)	3192 (50.9)	
Mild n (%)	4811 (40.7)	2156 (38.9)	2655 (42.3)	
Moderate n (%)	177 (1.5)	70 (1.3)	177 (1.7)	
Severe n (%)	303 (2.6)	139 (2.5)	164 (2.6)	
Very severe n (%)	237 (2)	80 (1.4)	157 (2.5)	
Smoking				< 0.001
Never n (%)	4363 (37.4)	1860 (33.9)	2503 (40.6)	
Former n (%)	4934 (42.3)	2577 (47.0)	2357 (38.2)	
Current n (%)	2355 (20.2)	1043 (19.0)	1312 (21.3)	
Alcohol				< 0.001
Never n (%)	5786 (52.4)	1849 (35)	3937 (68.2)	
Monthly n (%)	5021 (45.5)	3244 (61.4)	1777 (30.8)	
Weekly n (%)	240 (2.2)	190 (3.6)	50 (1)	
Exercise level				< 0.001
Easy n (%)	4978 (46.8)	2167 (42.9)	2811 (50.2)	
Moderate n (%)	5321 (50)	2650 (52.5)	2671 (47.7)	
Hard n (%)	346 (3.3)	230 (4.6)	116 (2.1)	

Education level				< 0.001
1 n (%)	3267 (28.0)	1335 (24.4)	1932 (31.2)	
2 n (%)	3038 (26.1)	1541 (28.2)	1497 (24.2)	
3 n (%)	862 (7.4)	390 (7.1)	862 (7.6)	
4 n (%)	2087 (17.9)	1147 (21.0)	940 (15.2)	
5 n (%)	2406 (20.6)	1059 (19.4)	1347 (21.8)	

Values are mean with standard deviation (SD), or number n with percentage of column (%)
BMI (Body Mass Index); SBP (Systolic blood pressure); DBP (Diastolic blood pressure) AFib (Atrial fibrillation); SaO_2 (Oxygen Saturation)
Education level:
1 (Primary/secondary school, modern secondary school)
2 (Technical school, vocational school, 1-2 years senior high school)
3 (High school diploma)
4 (College/university less than 4 years)
5(College/university 4 years or more)

In figure 2 and 3 the bar graph shows the proportion of total with no, mild, moderate, severe and very severe self-reported dyspnea distributed across 10 years age group and with each sex. Self reported dyspnea increased with increasing age.

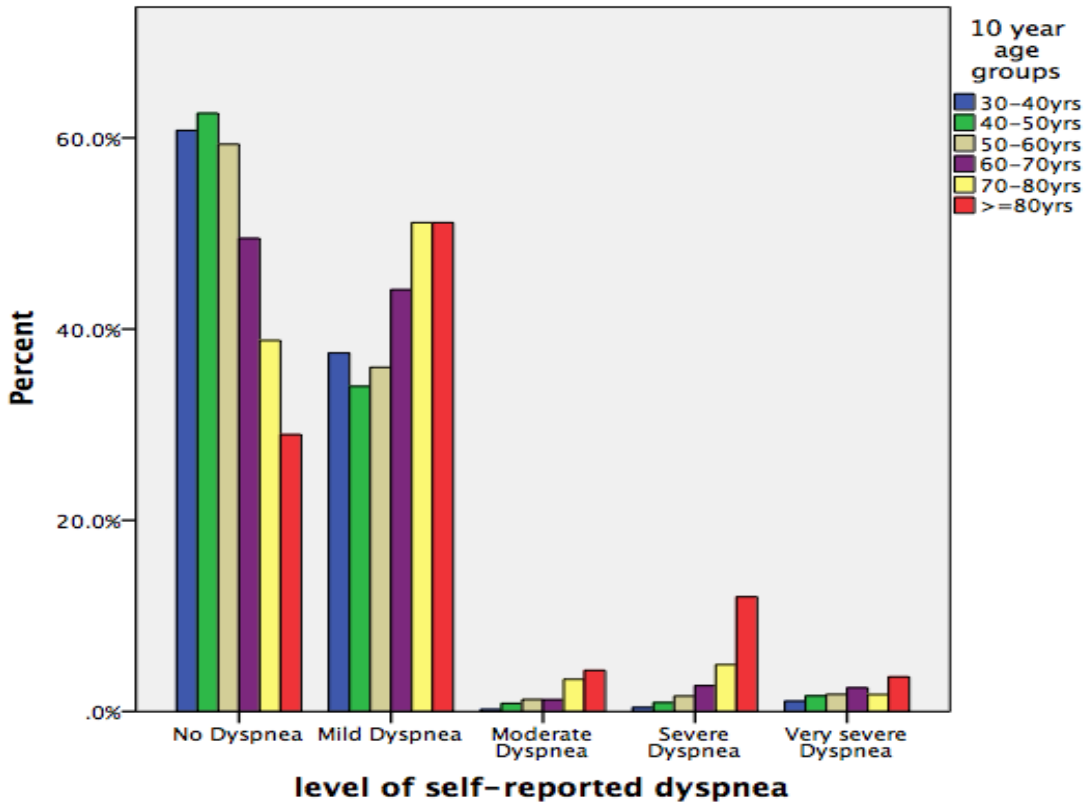

Figure 2: Proportion with no, mild, moderate, severe and very severe self-reported dyspnea distributed across 10 years age group

The participants aged 80 years or above reported the highest prevalence of dyspnea in all stages. The prevalence of dyspnea was increased with increasing age among female participants (Figure 3). Male participants also showed increased prevalence with increasing age but the prevalence of very severe dyspnea was almost same in all age group. Among the male participants with mild dyspnea prevalence was highest among those 70-80 years of age.

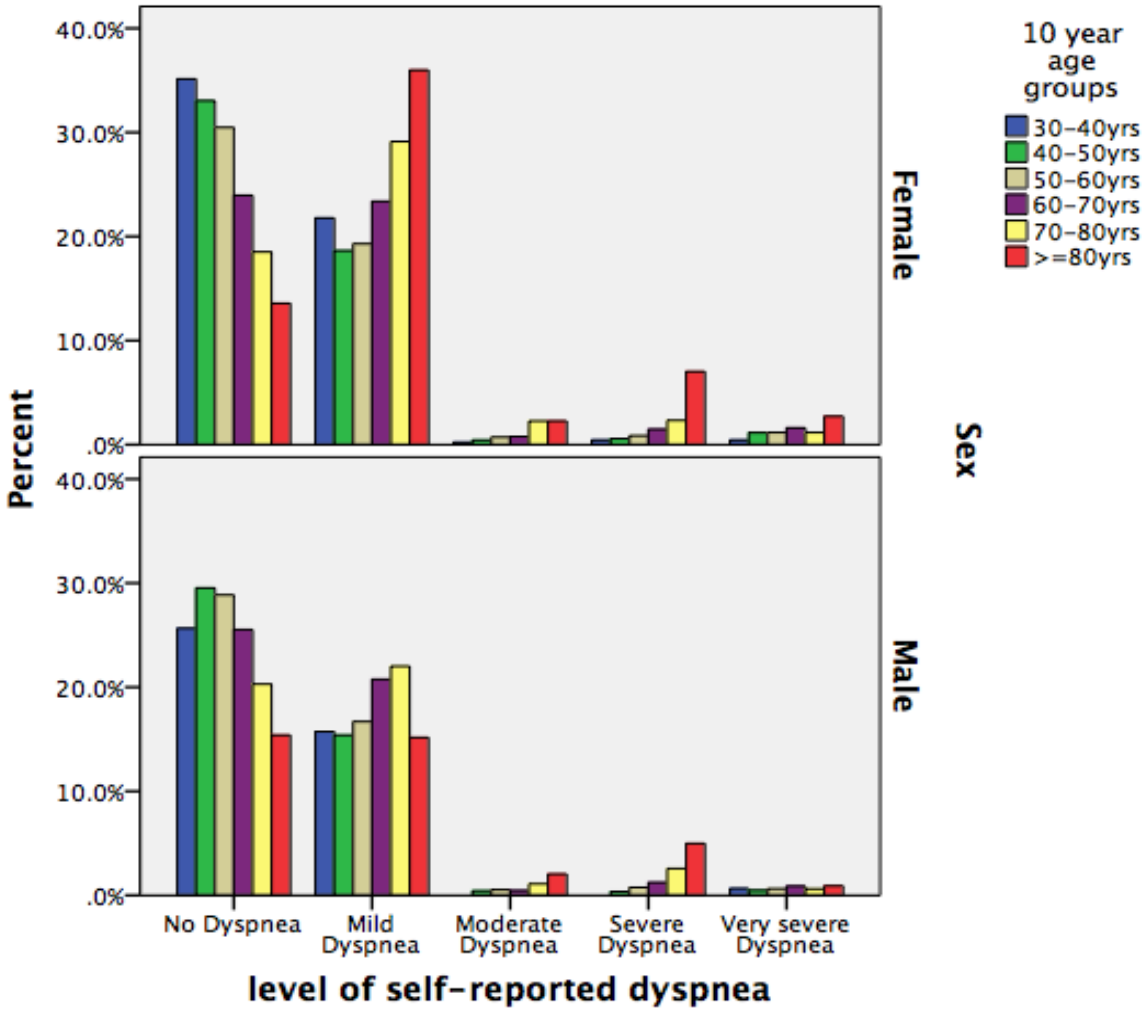

Figure 3: Proportion of total with each sex with no, mild, moderate, severe and very severe self-reported dyspnea distributed across 10 years age

Prevalence of dyspnea

Among men 23.4% had COPD and 6.2% had restrictive lung disease compared to 16.7% and 5.6% in women (Table 2). Among the participants with obstructive lung disease prevalence of dyspnea was higher among women compared to men (p value <0.001). With mild COPD, the prevalence of dyspnea was 50.5% for men and 57.5% for women. Among participants with moderate COPD prevalence of dyspnea was 67.3% for men and 75% for women. The prevalence of mild dyspnea was higher among participants with obstructive lung disease. The prevalence of mild dyspnea was 44.5%, 56.3%, 55.8% and 27.3% for men and 49.8%, 59.5%, 57.2% and 33.3% for women with mild, moderate, severe and very severe COPD respectively. Also, with restrictive lung disease prevalence of dyspnea was higher among women compared to men. Men with restrictive lung disease 65.7% reported dyspnea and women with restrictive lung disease 79% reported dyspnea. Most of these reported, mild dyspnea both in men 62.3% and women 67.7%. The prevalence of self-reported dyspnea categorized by level of left atrium diameter index by body surface area (LAD/BSA) is summarized in table 3. 18.6% of the participants had LAD/BSA above the normal upper reference limit of ≥2.3 cm/m^2. For these subject the prevalence of mild dyspnea was 20.9%, moderate dyspnea was 30%, severe dyspnea was 29.3% and very severe dyspnea 30.3% (p for trend <0.001). The prevalence of enlarged LAD/BSA increased from 15% in subjects without self-reported dyspnea to 30% in moderate dyspnea without further increase with increasing severity.

Table 2: Observed prevalence of self-reported dyspnea in the study population of men and women stratified by lung function by spirometry

Self-reported dyspnea	Total	Lung function by spirometry					
		Normal	**Mild COPD**	**Moderate COPD**	**Severe COPD**	**Very severe COPD**	**Restrictive Lung Disease**
Men valid n (%)	2488	1753 (70.4)	234 (9.4)	293 (11.8)	43 (1.8)	11 (0.4)	154 (6.2)
Women valid n (%)	3264	2534 (77.7)	233 (7.1)	279 (8.5)	35 (1.0)	3 (0.1)	180 (5.6)
No dyspnea							
Men n (%)	1294 (52)	1026 (58.5)	116 (49.5)	96 (32.7)	3 (7)	0 (0)	53 (34.3)
Women n (%)	1492 (45.8)	1279 (50.5)	99 (42.5)	70 (25)	5 (14.2)	1 (33.3)	38 (21)
Mild dyspnea							
Men n (%)	1051 (42.3)	659 (37.5)	104 (44.5)	165 (56.3)	24 (55.8)	3 (27.3)	96 (62.3)
Women n (%)	1508 (46.2)	1083 (42.7)	116 (49.8)	166 (59.5)	20 (57.2)	1 (33.3)	122 (67.7)
Moderate dyspnea							
Men n (%)	36 (1.4)	15 (1)	3 (1.3)	12 (4)	4 (9.4)	1 (9)	1 (1)
Women n (%)	75 (2.2)	48 (2)	3 (1.2)	13 (4.7)	4 (11.4)	0 (0)	7 (4)
Severe dyspnea							
Men n (%)	75 (3)	30 (1.7)	8 (3.5)	17 (6)	11 (25.5)	7 (63.7)	2 (1.2)
Women n (%)	98 (3)	55 (2.1)	10 (4.3)	19 (6.8)	6 (17.2)	1 (33.3)	7 (4)
Very severe dyspnea							
Men n (%)	32 (1.3)	23 (1.3)	3 (1.2)	3 (1)	1 (2.3)	0 (0)	2 (1.2)
Women n (%)	91 (2.8)	69 (2.7)	5 (2.2)	11 (4)	0 (0)	0 (0)	6 (3.3)
		P sex difference <0.001					

COPD (Chronic Obstructive Pulmonary Disease); Normal ($FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$predicted and $FVC \geq 80\%$predicted); Mild ($FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted); Moderate ($FEV_1/FVC < 0.7$ and $50\% \leq FEV_1 < 80\%$ predicted); Severe ($FEV_1/FVC < 0.7$ and $30\% \leq FEV_1 < 50\%$ predicted); Very severe ($FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted); Restrictive disease ($FEV_1/FVC \geq 0.7$ and $FEV_1 < 80\%$ or $FVC < 80\%$ predicted

Table 3: Observed prevalence of self-reported dyspnea in the study population categorized by level of Left atrium size

LA diameter/BSA (cm/m^2)	**Total**	**Self-Reported Dyspnea**					**P value**
		No Dyspnea	**Mild Dyspnea**	**Moderate Dyspnea**	**Severe Dyspnea**	**Very severe Dyspnea**	
Valid n (%)	2029	959 (47.3)	929 (45.8)	50 (2.5)	58 (2.9)	33 (1.6)	
< 2.3 n (%)	1652 (81.4)	818 (85.3)	735 (79.1)	35 (70.0)	41 (70.7)	23 (69.7)	< 0.001
≥ 2.3 n (%)	377 (18.6)	141 (14.7)	194 (20.9)	15 (30)	17 (29.3)	10 (30.3)	

BSA (Body Surface Area)
LA (Left atrial)

Table 4 summarizes the prevalence of self-reported dyspnea according to spirometer and echocardiography measurements. Among the participants with both spirometric and echocardiographic measurement 12.5% had only abnormal echocardiography, 20.9% had only abnormal spirometer and 5.6% had both abnormal spirometry and echocardiography. The prevalence of self-reported dyspnea was higher among participants with abnormal spirometer compared to all other groups. Among the participants reporting mild, moderate, severe and very severe dyspnea 25.2%, 34.1%, 35.6% and 20.8% respectively had abnormal spirometry measurement. Similarly, among the participants reporting very severe dyspnea 29.2% had abnormal echocardiography measurement and among the participants reporting with severe dyspnea 22.2% had both abnormal spirometry and echocardiography measurements. Only 25.2% of the participants reporting dyspnea symptoms had abnormal measurements (appendix 1). Among them only 43.6% of male subjects reporting dyspneic symptoms had abnormal measurements compared to 56.4% of women reporting dyspneic symptoms (Appendix 1). There was a significant difference in men and women and measurement status (Appendix 2) i.e. normal/abnormal according to whether or not they have symptoms i.e. dyspnea/ no dyspnea (p*value<0.001).

Table 4: Prevalence of self-reported dyspnea in the study population with Spirometer and Echocardiography measurements

Characteristic	Total	Self-Reported Dyspnea					P value
		No Dyspnea	Mild Dyspnea	Moderate Dyspnea	Severe Dyspnea	Very severe Dyspnea	
Valid n (%)	1764	830 (47.1)	824 (46.7)	41 (2.3)	45 (2.6)	24 (1.4)	< 0.001
Normal spirometer and Echo n (%)	1075 (60.9)	586 (70.6)	450 (54.6)	15 (36.6)	14 (31.1)	10 (41.7)	
Abnormal Echo n (%)	221 (12.5)	91 (11.0)	110 (13.3)	8 (19.5)	5 (11.1)	7 (29.2)	
Abnormal Spirometer n (%)	369 (20.9)	126 (15.2)	208 (25.2)	14 (34.1)	16 (35.6)	5 (20.8)	
Abnormal spirometer and Echo n (%)	99 (5.6)	27 (3.3)	56 (6.8)	4 (9.8)	10 (22.2)	2 (8.3)	

Echo (Echocardiography)
Normal spirometer and Echo ($FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ or $FVC \geq 80\%$ predicted and Left atrial <2.3 cm/m^2)
Abnormal Echo (Left atrial ≥ 2.3 cm/m^2)
Abnormal Spirometer with obstructive pattern ($FEV_1/FVC < 0.7$)
Abnormal Spirometer with obstructive pattern and Echo ($FEV_1/FVC<0.7$ and Left atrial ≥ 2.3 cm/m^2)

Logistic regression analysis

Table 5 summarizes the results of the Univariate and multivariable analysis of demographic factor associated with prevalence of dyspnea (Yes/No). Increase in age was associated with higher prevalence of dyspnea. In univariate analysis, age group 60-70years [OR=1.5; 95% CI: 1.2-1.9], 70-80 years [OR=2.4; 95% CI: 1.9-3.0] and 80 and above years [OR=3.8; 95% CI: 2.8-5.0) were significantly associated with increased prevalence of dyspnea. However in multivariate analysis, the age group 80 years and above [OR=1.5; 95% CI: 1.1-2.3] was significantly associated with increased prevalence of dyspnea. The prevalence of dyspnea increased 20% [OR=1.2; 95% CI: 1.1-1.3] in female compared to male. Participants with BMI≥30kg/m^2 (obesity) were 2.5 times more likely to have dyspnea compared to participants with BMI<25 [OR=2.5; 95% CI: 2.2-2.8]. Self-reported disease was also associated with higher prevalence of dyspnea. In multivariate analysis heart attack [OR=1.7; 95% CI: 1.3-2.2], atrial fibrillation [OR=1.6; 95% CI: 1.3-2.0], angina pectoris [OR=2.1; 95%CI: 1.6-2.8], asthma [OR=2.2; 95% CI: 1.8-2.6] and bronchitis [OR=3.6; 95% CI: 2.7-4.8] were significantly associated with increased prevalence of dyspnea. Smoking was also associated with increased prevalence of dyspnea. Current smoker [OR=1.8; 95% CI: 1.6-2.0] and former smoker [OR=1.2; 95% CI: 1.1-1.3] were significantly associated with increased prevalence of dyspnea. Weekly intake of alcohol was associated with increased prevalence of dyspnea by 1.4 times [OR=1.4; 95% CI: 1.1-1.9] compared to those who do not consume alcohol. Low level of exercise was associated with increased prevalence of dyspnea compared to high level of exercise. The participants with high level of education had low prevalence of dyspnea compared to low level of education i.e. college/university less than 4 years [OR=0.8; 95% CI: 0.7-0.9] and college/university more than 4 years [OR=0.6; 95% CI:0.5-0.6].

Table 5: Univariate and multivariate analysis of demographic factor associated with prevalence of dyspnea (Yes/No)

Determinants	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age group (10years)				
30-40 years (ref.)	1.0		1.0	
40-50 years	0.9 (0.7-1.1)	0.456	0.7 (0.5-0.9)	0.011
50-60 years	1.0 (0.8-1.3)	0.565	0.7 (0.5-0.9)	0.009
60-70 years	1.5 (1.2-1.9)	<0.001	0.9 (0.7-1.1)	0.487
70-80 years	2.4 (1.9-3.0)	<0.001	1.0 (0.7-1.3)	0.920
80 and above years	3.8 (2.8-5.0)	<0.001	1.5 (1.1-2.3)	0.024
Sex				
Male (ref.)	1.0		1.0	
Female	1.2 (1.1-1.3)	<0.001	1.2 (1.1-1.4)	<0.001
Body mass index				
BMI <25 (ref.)	1.0		1.0	
BMI 25-29	1.6 (1.5-1.8)	<0.001	1.8 (1.6-2.0)	<0.001
BMI ≥30	2.5 (2.3-2.7)	<0.001	2.5 (2.2-2.8)	<0.001
Self-reported disease				
Diabetes				
No (ref.)	1.0			
Yes	1.8 (1.5-2.2)	<0.001		
Heart attack				
No (ref.)	1.0		1.0	
Yes	2.8 (2.3-3.3)	<0.001	1.7 (1.3-2.2)	<0.001
Atrial fibrillation				
No (ref.)	1.0		1.0	
Yes	2.4 (2.0-2.8)	<0.001	1.6 (1.3-2.0)	<0.001
Angina pectoris				
No (ref.)	1.0		1.0	
Yes	4.0 (3.3-4.9)	<0.001	2.1 (1.6-2.8)	<0.001
Asthma				
No (ref.)	1.0		1.0	
Yes	2.5 (2.2-2.9)	<0.001	2.2 (1.8-2.6)	<0.001
Bronchitis				
No (ref.)	1.0		1.0	
Yes	6.5 (5.1-8.3)	< 0.001	3.6 (2.7-4.8)	<0.001
Smoking				
Never (ref.)	1.0		1.0	
Former	1.5 (1.3-1.6)	<0.001	1.2 (1.1-1.3)	<0.001
Current	2.2 (2.0-2.4)	<0.001	1.8 (1.6-2.0)	<0.001
Alcohol				
Never (ref.)	1.0		1.0	
Monthly	0.8 (0.7-0.9)	<0.001	0.6 (0.5-1.4)	0.095
Weekly	1.1 (0.8-1.4)	0.274	1.4 (1.1-1.9)	0.016
Exercise level				
Easy	4.6 (3.5-6.0)	<0.001	2.9 (2.1-3.9)	<0.001
Moderate	2.1 (1.6-2.7)	<0.001	1.6 (1.2-2.1)	0.001
Hard (ref.)	1.0		1.0	

Education				
1 (ref.)	1.0		1.0	
2	0.7 (0.6-0.7)	<0.001	0.9 (0.8-1.0)	0.360
3	0.5 (0.4-0.6)	<0.001	0.8 (0.7-1.0)	0.166
4	0.5 (0.4-0.5)	<0.001	0.8 (0.7-0.9)	0.011
5	0.3 (0.2-0.3)	<0.001	0.6 (0.5-0.6)	<0.001

OR (Odd Ratio); (ref.) reference group. 1(Primary/secondary school, modern secondary school); 2 (Technical school, vocational school, 1-2 years senior high school); 3 (High school diploma); 4 (College/university less than 4 years); 5 (College/university 4 years or more).

Table 6: Univariate and multivariable analysis of level of COPD, Restrictive disease and spirometer and echocardiography measurements group associated with prevalence of dyspnea (Yes/No) with age and sex adjustment.

Determinants	**Univariate analysis**		**Multivariable analysis**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Level of COPD				
Normal (ref.)	1.0		1.0	
Mild	1.2 (1.1-1.5)	0.017	1.2 (0.7-2.2)	0.361
Moderate	2.6 (2.1-3.1)	<0.001	2.6 (1.5-4.5)	<0.001
Severe	9.4 (4.5-19.6)	<0.001	9.1 (2.0-44.7)	0.004
Very severe	13.9 (1.8-107.1)	0.011	6 (0.6-58.2)	0.121
Restrictive disease				
No (ref.)	1.0		1.0	
Yes	2.6 (2.0-3.3)	<0.001	2.8 (1.5-58.2)	<0.001
Measurement group				
Normal spirometer and echo (ref.)	1.0		1.0	
Abnormal echo	1.7 (1.2-2.2)	<0.001	1.3 (1.2-2.2)	<0.001
Abnormal spirometer	2.3 (1.8-2.9)	<0.001	1.7 (1.4-2.1)	<0.001
Abnormal spirometer and echo	3.1 (2.0-5.0)	0.003	2.0 (1.7-4.8)	0.003

OR (Odd Ratio); (ref.) reference group. Normal spirometer and Echo ($FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ or $FVC \geq 80\%$ predicted and Left atrial <2.3 cm/m^2); Abnormal Echo (Left atrial ≥ 2.3 cm/m^2); Abnormal Spirometer with obstructive pattern ($FEV_1/FVC < 0.7$); Abnormal Spirometer with obstructive pattern and Echo ($FEV_1/FVC<0.7$ and Left atrial ≥ 2.3 cm/m^2)

Table 6 summarizes univariate and multivariable analysis of level of COPD, Restrictive disease and spirometry and echocardiographic measurement group associated with prevalence of dyspnea (Yes/No) with age and sex adjustment. Increase in severity of COPD was associated with increased prevalence of dyspnea. Moderate COPD [OR=2.6; 95% CI: 1.5-4.5] and severe COPD [OR=9.4; 95% CI: 2.0-44.7] were significantly associated with increased prevalence of dyspnea. The prevalence of dyspnea increased 2.8 folds [OR=2.8; 95% CI: 1.5-5.2] in people with restrictive disease. In terms of spirometric and echocardiographic measurements, prevalence of dyspnea increased 1.3 folds [OR=1.3; 95% CI: 1.2-2.2] in people with abnormal echo compared to people with both normal spirometer and echocardiography. Also, prevalence of dyspnea increased 1.7 folds [OR=1.7; 95% CI: 1.4-2.1] in people with abnormal spirometry compared to people with both normal spirometry and echocardiography. Similarly, prevalence of dyspnea increased 2 folds [OR=2; 95% CI: 1.7-4.8] in people with abnormal spirometry and echocardiography compared to people with both normal spirometry and echocardiography.

7. DISCUSSION

We observed that prevalence of dyspnea was related to cardiac or respiratory measure of disease and dyspnea differ in general characteristics from those not reporting dyspnea which might be explained by known risk factor such as age, sex, smoking habits, alcohol intake and comorbidity.

In this study, we observed a higher self-reported prevalence of dyspnea (Table 1) among men and women. A higher prevalence of obesity (Table 1) among men and women in our study might explain higher prevalence of self-reported dyspnea in men and women in our study because several studies such as the large epidemiological study of 16,171 American adults aged ≥17 years (50) showed a positive association between BMI and self-reported prevalence of dyspnea and Zutler et al. (51) recently reported that obesity was associated with a 3.6 fold increased risk of dyspnea on exertion independent of age, sex and airway obstruction. Similarly, the high proportion of men and women reporting former and current smoking and self-reported asthma and heart attack is associated with higher self-reported prevalence of dyspnea. We observed prevalence rate of dyspnea by different age group and gender (Figure 2 and 3). Women reported a higher self-reported prevalence of dyspnea compared to men. However, we observe that increasing age had a stronger influence on the prevalence of dyspnea than gender. The participants with higher age group were associated with higher Self-reported prevalence of dyspnea in our study and dyspnea was seen common in both men and women participant's aged ≥80 years. One might consider dyspnea rather a normal phenomenon in the aged, as dyspnea is so common in older people. There was a marked gender difference in dyspnea prevalence with predisposing factors, such as smoking, more frequently encountered in women in this study. Similar to our studies other studies have found increased rates of breathlessness in women compared to men (52-54). This gender differences in reported symptoms is the subject of ongoing debate but might be consider as a true difference in prevalence (52).

We observe a large gender difference in COPD (Table 2) as cause of symptoms, which might be due to differences in smoking history. In our study, increase in the severity of COPD as cause of symptoms was seen with increased prevalence of dyspnea for both men and women and also prevalence of

dyspnea was higher among men and women with restrictive lung disease as cause of symptoms. Similarly, in participants with abnormal LA measurement, a measure linked to heart failure, 63% reported dyspnea as compared to only 50% in those with normal or moderately enlarged LA size (Table 3). However, as we also observed self-reported dyspnea among participants with normal LA measurements, this might be due to the presence of other risk factor. Three studies looked at dyspnea in the general population with a mean age 62 years but age ranged from 15 to 95 years (55-57). In these three studies, cardiac and/or pulmonary diseases were the reason of dyspnea in 60%, with the most common underlying diagnosis being heart failure and COPD. This is comparable with our study with participants at a mean age of 57 years, with a cardiac and / or pulmonary disease as reason of dyspnea in 67.5% of men with moderate COPD and 75% of women with moderate COPD and 30.3% with abnormal LA measurement i.e. diastolic heart failure respectively. Therefore, heart failure and COPD were the most common underlying diagnosis in cardiac and /or pulmonary disease being the reason of dyspnea in our study. Also, we observed higher prevalence of dyspnea in women with COPD compared to men with COPD, which might be due to large gender difference in COPD as mention above and might be due to difference in smoking history.

Different recommendations exist regarding diagnostic strategies in the evaluation of dyspnea. The most frequently recommended screening tests are spirometry, echocardiography and chest radiography (55). As respiratory and/or heart disease was frequently the cause of dyspnea, spiromery and/or echocardiography should obviously be one of the initial screening tests. Among the participants with both spirometry and echocardiography measurement, we observed abnormal spirometry and/ or echocardiography in 39% of the participants (Table 4) and high proportion of participants (25.2%) reporting dyspnea symptoms had abnormal measurements (appendix 1). We observed a larger gender difference in reporting dyspnea symptoms among participants with abnormal spirometry, which might be due to differences in lung geometry between the sexes, because females, on average, would be expected to have smaller airways and smaller lung volumes than male (58). Also, difference in smoking history because with the increase in smoking pack years being associated with decrease

FEV_1, FEV_1% predicted and FEV_1/FVC values in both male and female (59). Furthermore, a study carried out by Prescott and colleagues (60) demonstrated that female smokers had greater reductions in FEV_1 than males at comparable level of smoking intensity, which might be the reason why we observed more women participants with abnormal spirometry.

We carried out a univariate and multivariable logistic regression analysis between dyspnea and several covariates and found strong associations between them. The oldest age group was marked with increased prevalence of dyspnea. Similarly, Overall prevalence of dyspnea was greater for women. Obesity was associated with a 2.5 fold-increased risk of dyspnea. The participants with self-reported disease such as diabetes, atrial fibrillation, angina pectoris, heart attack, asthma and bronchitis were associated with increased prevalence of dyspnea but in multivariable analysis diabetes was not significantly associated with dyspnea. We observe smoking and alcohol intake as significantly associated with a higher prevalence of dyspnea. As compared to a high level of exercise, moderate and sedentary exercise levels were associated with a 60% and tripling of the odds for reporting dyspnea. Increasing length of education was also significantly associated with a decreasing prevalence of self-reported dyspnea. Similar to our study a population survey assessing the prevalence and severity of dyspnea in adults (17) found age, gender and education associated with dyspnea. We observed 9.1 fold increase in odds of self-reported dyspnea with increased severity of COPD. A restrictive disease pattern had a 2.8 fold increase similar to the results in the study by Jakeways and colleagues (21).

Strength and limitations

Selection bias could be a limitation of our study as echocardiography only was performed in a subgroup. But as this subgroup was randomly selected from the larger the main limitations caused by the lower number in the groups eligible for this analysis is lower precision of our prevalence estimates and lower power in the multivariable logistic regression analysis. There were relatively high number of participants without both measurement of lung function (spirometry) and echocardiography among study eligible participants in our study. The exclusion of these participants from our study analysis might have affected our results to better explore how dyspnea is related to cardiac and respiratory

measure of disease because there might be a significant difference between the subgroup with spirometry and echocardiography as compared to those with echocardiography, which we could not include in the analysis. We used measurement of left atrium size to identify participants with diastolic heart failure however there were relatively few eligible participants with LV systolic dysfunction a more severe form of heart failure. The selection bias due to missing echocardiography or spirometric measurements might have affected our results regarding the impact of cardiac or pulmonary disease on dyspnea, as COPD and systolic heart failure are known to coexist (61). A study carried out by Currow and colleagues (17) found work status and income a significant predictor of breathlessness. However, this study was unable to analyze the role of these variables.

The main strength of this study is the large sample size, where all the participants with self-reported dyspnea in municipality of Tromsø were included providing a sample size with power to perform a stratified analysis bye age and sex, to show at least any trends of differences in the prevalence of dyspnea and how dyspnea differ in general characteristics from those not reporting dyspnea.

8. CONCLUSION

Our study shows a strong association between self-reported dyspnea and diastolic heart failure, restrictive pulmonary disease and increasing levels of COPD. In addition obesity, lack of physical activity, smoking and self-reported cardiac disease such as atrial fibrillation, myocardial infraction and angina and pulmonary disease such as asthma and bronchitis independently of spirometric and echocardiographic values. This indicate a large potential for prevention of self-reported dyspnea by addressing life style and other measure that will prevent cardiovascular and pulmonary disease both in an individual and public health level.

9. RECOMMENDATION

All the patients with self-reported dyspnea should be acknowledged and the physicians should assess if all individuals identified with having dyspnea have COPD, CHD or heart failure as a cause of symptoms. Health service utilization should facilitate the assessment of policies for monitoring of dyspnea particularly in elderly population and supporting care of population living with dyspnea related to COPD, CHD and heart failure. Larger studies and research are needed to examine whether the possible treatable causes of dyspnea will translate into improved patient outcome in elderly people as the balance between positive effects and side effects of treatment might be different in this particular group of patients.

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11. APPENDICES

Appendix 1

Table 7: Demographic and baseline characteristics in study population stratified by measurement group

Characteristics	**Total**	**Spirometer and Echo measurement group**				**P value**
		Normal spirometer and Echo	**Abnormal Echo**	**Abnormal spirometer**	**Abnormal spirometer and Echo**	
Valid n (%)	1764	1075 (60.9)	221 (12.5)	369 (20.9)	99 (5.6)	
Age (SD)	65 (11.1)	62 (10.8)	70 (9.7)	67 (10)	75 (8.3)	< 0.001
Male n (%)	780 (44.2)	458 (42.6)	70 (31.7)	215 (58.3)	37 (37.4)	< 0.001
Measurement						
Mean SBP (SD)	143.2 (24)	139.4 (22)	153.2 (25)	145.1 (25.7)	155.5 (24.6)	< 0.001
Mean DBP (SD)	78.6 (10.6)	78.5 (10)	79.3 (11.4)	78.7 (11.1)	77.9 (12.2)	0.444
BMI kg/m^2 (SD)	27 (4)	27.1 (4.1)	26.8 (3.9)	26.8 (4.1)	26.7 (4.1)	0.633
BMI kg/m^2 category						<0.001
BMI<25 n (%)	582 (33%)	343 (31.9)	70 (31.7)	130 (35.2)	39 (39.4)	
BMI 25-29 n (%)	823 (46.7)	503 (46.8)	108 (48.9)	170 (46.1)	42 (42.4)	
BMI ≥ 30 n (%)	359 (20.4)	229 (21.3)	43 (19.5)	69 (18.7)	18 (18.2)	
SaO_2 (SD)	97.4 (1.8)	97.6 (1.2)	97.6 (1.2)	96.8 (3.2)	97.2 (1.3)	<0.001
Cholesterol (SD)	5.6 (1.1)	5.7 (1)	5.7 (1.1)	5.6 (1.1)	5.5 (1)	0.784
Glucose (SD)	5.5 (1.5)	5.5 (1.5)	5.4 (1.2)	5.6 (1.6)	5.5 (1.3)	0.530
Heart rate (SD)	64.9 (10.3)	64.8 (10)	64.4 (10)	65.4 (10.7)	65 (13)	0.877
Self-reported disease						
Diabetes n (%)	97 (5.6)	58 (5.5)	16 (7.4)	19 (5.3)	4 (4.3)	0.623
Heart attack n (%)	142 (8.2)	55 (5.2)	22 (10.0)	46 (12.8)	19 (20.7)	< 0.001
Atrial fibrillation n (%)	137 (8.1)	55 (5.3)	34 (16.0)	24 (6.9)	24 (25.3)	0.003
Angina pectoris n (%)	135 (7.9)	52 (4.9)	35 (16.4)	30 (8.4)	18 (19.6)	< 0.001
Asthma n (%)	191 (11.1)	90 (8.5)	16 (7.4)	69 (19.4)	16 (17.6)	< 0.001
Bronchitis n (%)	79 (4.6)	23 (2.3)	8 (3.7)	32 (9.0)	16 (17.4)	< 0.001

Smoking						< 0.001
Never n (%)	632 (35.8)	427 (40.2)	102 (47.4)	69 (19.1)	34 (34.7)	
Former n (%)	803 (45.5)	481 (45.3)	91 (42.3)	185 (51.1)	46 (46.9)	
Current n (%)	329 (18.7)	153 (14.4)	32 (10.2)	116 (29.8)	28 (18.4)	
Alcohol						< 0.001
Never n (%)	1032 (58.5)	609 (60.4)	149 (56.8)	208 (57.3)	66 (50.0)	
Monthly n (%)	601 (34.1)	370 (36.7)	68 (25.9)	124 (34.1)	39 (29.5)	
Weekly n (%)	131 (7.4)	28 (2.9)	45 (17.3)	31 (8.6)	27(20.5)	
Exercise level						< 0.001
Easy n (%)	976 (55.3)	504 (51.7)	169 (59.7)	227 (60.0)	76 (59.4)	
Moderate n (%)	739 (41.9)	443 (45.5)	108 (38.2)	144 (38.1)	44 (34.4)	
Hard n (%)	49 (2.8)	28 (2.8)	6 (2.1)	7 (1.9)	8 (6.2)	
Education						< 0.001
1 n (%)	632 (36.5)	336 (31.6)	100 (46.9)	139 (38.6)	57 (59.4)	
2 n (%)	486 (28.0)	294 (27.6)	61 (28.6)	110 (30.6)	21 (21.9)	
3 n (%)	112 (5.9)	68 (6.4)	12 (3.3)	23 (6.4)	9(4.2)	
4 n (%)	273 (15.8)	189 (17.8)	24 (11.3)	49 (13.6)	11 (11.3)	
5 n (%)	261 (13.8)	198 (16.6)	21 (9.9)	39 (10.8)	3 (3.1)	

Echo (Echocardiography)
Normal spirometer and Echo ($FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ or $FVC \geq 80\%$ predicted and Left atrial <2.29 cm/m^2)
Abnormal Echo (Left atrial ≥ 2.3 cm/m^2); Abnormal Spirometer ($FEV_1/FVC < 0.7$); Abnormal Spirometer and Echo ($FEV_1/FVC<0.7$ and Left atrial ≥ 3.0 cm/m^2)
Values are mean (SD) when appropriate; BMI (Body Mass Index)

Appendix 2

Table 8: Demographic and baseline characteristics in study population with and without dyspnea stratified by normal and abnormal measurement group

Characteristics	**Total**	**No dyspnea**		**P value**	**Dyspnea**		**P value**	**P* value**
		Normal	Abnormal		Normal	Abnormal		
Valid n (%)	1764	586 (33.2)	244 (13.8)		489 (27.7)	445 (25.2)		
Age (SD)	65 (11.1)	60.7 (10.8)	67.6 (10.2)	<0.001	64.1 (10.6)	70.1 (9.9)	<0.001	<0 .001
Male n (%)	780 (44.2)	265 (45.2)	128 (52.5)	0.057	193 (39.5)	194 (43.6)	0.201	< 0.001
Measurement								
Mean SBP (SD)	143.2 (24)	137.2 (20.4)	149.7 (25)	<0.001	142 (23.6)	148.4 (26)	0.007	< 0.001
Mean DBP (SD)	78.6 (10.6)	78.6 (10)	79.7 (10.8)	0.056	78.4 (10.1)	78.24 (11.7)	0.016	0.335
BMI kg/m^2 (SD)	27 (4)	26.1 (3.6)	26.2 (3.7)	0.155	28.2 (4.3)	27.1 (4.1)	0.028	< 0.001
BMI kg/m^2 category				<0.001			<0.001	<0.001
BMI <25 n (%)	582 (33%)	235 (40.1)	102 (41.8)		108 (22.1)	137 (30.7)		
BMI 25-29 n (%)	823 (46.7)	264 (45.1)	105 (43)		239 (48.9)	215 (48.3)		
BMI ≥ 30 n (%)	359 (20.4)	87 (14.8)	37 (15.2)		142 (29)	93 (20.9)		
So_2 (SD)	97.4 (1.8)	97.8 (1.2)	97.6 (1)	0.225	97.5 (1.1)	96.8 (2.9)	0.02	< 0.001
Cholesterol (SD)	5.6 (1.1)	5.7 (1)	5.6 (1)	0.036	5.7 (1.1)	5.5 (1.1)	0.056	0.066
Glucose (SD)	5.5 (1.5)	5.4 (1.6)	5.5 (1.4)	0.012	5.5 (1.3)	5.6 (1.5)	0.408	0.016
Heart rate (SD)	64.9 (10.3)	64.1 (9.8)	64.2 (10.9)	0.514	65.6 (10.1)	65.5 (10.8)	0.987	0.023
Self-reported disease								
Diabetes n (%)	97 (5.6)	20 (3.5)	14 (5.8)	0.122	38 (8)	25 (5.8)	0.206	0.836
Heart attack n (%)	142 (8.2)	23 (4.0)	17 (7.0)	0.068	32 (6.7)	70 (16.4)	<0.001	< 0.001
Atrial fibrillation n (%)	137 (8.1)	22 (3.8)	20 (8.3)	0.008	33 (7)	62 (14.9)	<0.001	0.002
Angina pectoris n (%)	135 (7.9)	16 (2.8)	17 (7.1)	0.004	36 (7.6)	66 (15.6)	<0.001	<0.001
Asthma n (%)	191 (11.1)	28 (4.8)	20 (8.3)	0.052	62 (13.0)	81 (19.2)	0.012	< 0.001
Bronchitis n (%)	79 (4.6)	4 (0.7)	4 (1.7)	0.2	19 (4.0)	52 (12.4)	<0.001	< 0.001

Smoking				0.216		<0.001	<0.001
Never n (%)	632 (35.8)	243 (41.8)	89 (33.2)		184 (38.4)	116 (26.7)	
Former n (%)	803 (45.5)	262 (45.0)	109 (40.6)		219 (45.7)	213 (49)	
Current n (%)	329 (18.7)	77 (13.2)	70 (26.2)		76 (15.9)	106 (24.4)	
Alcohol				0.343		0.021	0.003
Never n (%)	1032 (58.5)	328 (59.4)	141 (49.8)		281 (61.8)	282 (59.4)	
Monthly n (%)	601 (34.1)	214 (38.7)	97 (34.2)		156 (34.2)	134 (28.3)	
Weekly n (%)	131(7.4)	10 (1.9)	45 (16)		18 (4)	58 (12.3)	
Exercise level				0.017		0.032	<0.001
Easy n (%)	976 (55.3)	247 (44.8)	169 (52.8)		257 (60.8)	303 (64.6)	
Moderate n (%)	739 (41.9)	282 (51)	139 (43.4)		161 (38)	157 (33.4)	
Hard n (%)	49 (2.8)	23 (4.2)	12 (3.8)		5 (1.2)	9 (2)	
Education				<0.001		0.003	<0.001
1 n (%)	632 (35.8)	160 (27)	94 (38.8)		176 (35.6)	202 (46.2)	
2 n (%)	486 (27.6)	153 (25.9)	64 (26.5)		141 (28.5)	128 (29.2)	
3 n (%)	112 (6.4)	38 (6.4)	26 (10.8)		30 (6)	18 (4.2)	
4 n (%)	273 (15.4)	108 (18.3)	30 (12.4)		81 (16.4)	54 (12.4)	
5 n (%)	261 (14.8)	132 (22.4)	28 8 (11.5)		66 (13.5)	35 (8)	

Echo (Echocardiography). Normal (normal spirometer and Echo i.e.$FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ or $FVC \geq 80\%$ predicted and Left atrial <2.29 cm/m^2); Abnormal (abnormal Echo i.e. Left atrial ≥ 3.0 cm/m^2, abnormal spirometer i.e. $FEV_1/FVC < 0.7$ and abnormal spirometer and echo i.e. $FEV_1/FVC<0.7$ and Left atrial ≥ 3.0 cm/m^2); Values are mean with standard deviation (SD), or number n with percentage of column (%)BMI (Body Mass Index). SBP (Systolic blood pressure). DBP (Diastolic blood pressure) Education level: 1 (Primary/secondary school, modern secondary school); 2 (Technical school, vocational school, 1-2 years senior high school);
3 (High school diploma); 4 (College/university less than 4 years); 5 (College/university 4 years or more). AF (Atrial fibrillation); SO_2 (Oxygen Saturation); P* (overall p value i.e. whether there are differences in effects on measurement status according to whether or not they have symptoms)