Marlen Knutli

Anxiety and depression symptoms in relation to lung function and Chronic Obstructive Pulmonary Disease (COPD) in 9000 adults. The HUNT 2 (1995-97) population study

Master's Thesis in Clinical Health Science,

Clinical research

Norges teknisk-naturvitenskapelige universitet

Det medisinske fakultet

Institutt for samfunnsmedisin

Trondheim, January 2014

Forord

Denne studien er utført i forbindelse med masterstudiet i Klinisk helsevitenskap ved NTNU, Trondheim.

Jeg ønsker å takke Helseundersøkelsen i Nord-Trøndelag (HUNT) for muligheten til å bruke data fra HUNT 2 til oppgaven. HUNT er et samarbeidsprosjekt mellom HUNT forskningssenter (Det medisinske fakultet, Norges teknisk-naturvitenskapelige universitet, NTNU), Nord-Trøndelag fylkeskommune, Helse Midt Norge og Nasjonalt folkehelseinstitutt.

Takk til ansvarlig veileder, 1 Amanuensis, Dr.med. Ottar Bjerkeset for god oppfølging, tålmodighet, konstruktive tilbakemeldinger og gode diskusjoner.

En takk går også til biveileder overlege Thor Naustdal for tilbakemeldinger, spesielt på tema KOLS og hjelp i forhold til tolkning av spirometriverdier. Takk til Ulla Romild, som har hjulpet meg inn i statistikkens verden.

Takk til mine gode kollegaer i Forsknings- og utviklingsavdelingen ved Helse Nord-Trøndelag for god støtte i studieperioden.

Takk til familie og venner for støtte.

Sist men ikke minst vil jeg takke mine to flotte ungdommer, Stine Marie og Kristoffer, og min kjære Rolf Inge, for tålmodighet og støtte!

Januar 2014

Marlen Knutli

Abstract

Background: Anxiety and depression symptoms are highly prevalent in people with Chronic Obstructive Pulmonary Disease (COPD). However, there are few large studies of the general population that have investigated the association of anxiety and depression with lung function.

Purpose: To investigate the relationship between anxiety and depression symptoms and lung function in a large adult population sample.

Materials and methods: In this cross-sectional study we included 8,981 men and women from the Nord-Trøndelags Health Study, HUNT2 (1995-97), Norway. Symptoms of anxiety and depression were self-reported using the Hospital Anxiety and Depression Scale (HADS). Lung function was defined by spirometric values and categorized by GOLD – classification.

Results: Participants with moderate and severe COPD had significant higher crude odds ratio for pure depression and mixed symptoms, yet this was mainly explained by differences in age and gender between the groups. In gender-stratified analysis women had increased odds for symptoms of depression and mixed symptoms due to exacerbated lung function. In contrast, men with severe COPD reported higher rates of symptoms of pure anxiety. However, statistical evidence was borderline in the fully adjusted models.

Conclusion: Results from this study indicate a high prevalence of mental distress in severe COPD. Gender specific relations between symptoms of anxiety and depression and lung function was found; worsened lung function was associated with pure depression and mixed symptoms in women, while severe COPD was associated with pure anxiety in men. .These patterns might have clinical relevance and should be further investigated.

Relevance: Untreated depression is known to have unfavorable impact on compliance with medical treatment, length of stay in hospitals, number of primary care consultations, symptom burden and decreased quality of life among others. Our findings indicate that psychological treatment, in particular aiming at depressive symptoms, might have a potential to improve quality of life, adherence to treatment and outcome in COPD.

Contents

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with chronic inflammation in the airways (1). The combination of chronic obstructive bronchitis and emphysema are the main factors for developing COPD, primarily caused by smoking. Smoking is well known to have a negative effect on lung function in general (2).

Despite the challenge of estimating prevalence of COPD across cultural and research settings, the global prevalence is estimated to be approximately 10%, yet it is underlined that this is probably an underestimation. COPD is, according to Global Initiative for Chronic Obstructive Lung Disease (GOLD), the fourth most common cause of death worldwide (1).

Earlier COPD were more prevalent among men than women, but increased smoking among women in high-income countries has now resulted in more equal prevalence of COPD between the genders (3).

Anxiety and depression are the two of most prevalent mental health conditions in adults, and both have a negative impact on health and quality of life in both the general population and among people with COPD, though the prevalence of anxiety and depression seems to be higher in the COPD population (4, 5).

Lifetime prevalence of any anxiety and any mood disorder in the general population of European countries have been estimated to 13.6% and 12.8%, respectively, whereas the 12 month prevalence for the same diagnoses were 6.4% and 4.2% (6). The US based Epidemiologic Catchment Area program (ECA) reported somewhat higher 12 months prevalence; 12.7 % for any anxiety disorder and 5.1 % for any mood disorder in American normal population (7).

Both anxiety and depression have shown great overlap with COPD (5, 8-12), and overall they seem to increase with severity of COPD (10). Most studies (8, 13-15) that have found associations of COPD with anxiety and depression were carried out in hospital settings or in rehabilitation groups, yet evidence from large scale population based studies are lacking. A review by Mikkelsen et al (9), states that despite the high prevalence of, and great impact on public health, anxiety and depression in COPD are largely ignored, or interpreted as a natural development of the pulmonary disease.

A review by Hill et al. (8) emphasizes that anxiety and depression represent separate constructs, although they often coexist. Result of this review suggests that anxiety and depression influence behavior and management of COPD differentially. In those with anxiety, smoking and dyspnea are highly associated with COPD. Complex interrelationships between dyspnea and anxiety further contribute to the high prevalence of anxiety in COPD (8). Smoking assessment and pulmonary rehabilitation, for example supervised exercise training, might reduce anxiety. It is known that people with COPD experience loss of function in several areas of their lives, and such experiences reinforce the feeling of hopelessness; lack of motivation and social withdrawal, which in may lead to depression. In COPD patients, psychotherapy combined with physical therapy have improved depression scores (8). A clinical study performed by Wilhelm et al (16) conclude that it is a challenge to identify the underpinning mechanisms linking respiration and specific clinical symptoms of anxiety, but they underline the importance of respiratory physiology for understanding panic disorder.

A former study of this HUNT 2 cohort examined the associations between objective lung function, self-reported symptoms of anxiety and self-perceived dyspnea (17). They found that people with anxiety were more likely to report dyspnea than people without anxiety across all COPD stages. This suggests that the subjective experience of breathing discomfort, related to reduce lung function, can also influence or be influenced by anxiety. Despite the fact that anxiety and depression symptoms show great overlap, few previous studies have studied the association of symptoms of pure anxiety, pure depression and mixed symptoms with stage of COPD.

The aim of the study is to study self-reported symptoms of anxiety and depression, separately and mixed, in association with lung function in 8,981 Norwegian adults who participated in the HUNT 2 study.

Theoretical background

Chronic Obstructive Pulmonary Disease (COPD) is a collective term for diseases characterized by airway resistance, which is not fully reversible. Chronic obstructive bronchitis, a state of chronic cough and increased production of sputum, and emphysema, caused by reduced elastic rebound effect, represents the majority of the COPD diagnoses (2). Early stages of COPD may often be perceived as symptom free, even though a lasting cough with sputum is reported. Later symptoms like dyspnea, wheezing, infections, and frequent episodes with sputum are common (2, 18). COPD is often diagnosed late. One reason for this

can be that people adjust to decreasing lung function and don't see a doctor and get a spirometry examination done before they have severe symptoms (18). COPD is associated with poor quality of life (QoL), higher risk of weight loss, muscular atrophy, cardiovascular disease, anemia and depression (2, 19, 20).Comorbidity, high mortality and increased length of stay (LOS) in hospitals are other outcomes that are associated with chronic obstructive pulmonary disease (9).

COPD is categorized as an epidemic disease (3). In Norway approximately 4% of the population has COPD, with an incidence of 0.4% per year (21). In the Nordic countries, it is suggested that 7-14% of the adult population have COPD (2). The global prevalence of moderate or higher stages of COPD is estimated to be 10.1% by Buist et al. (22). However, there are varies in prevalence worldwide depending on smoking habits, indoor air pollution and age within the population (23). Also, economic, distance dependent factors and lack of medical service in developing countries are possible obstacles for estimating a worldwide prevalence of COPD. People having COPD without symptoms are another issue for not being able to estimate a global prevalence. Other prevalence variation would be in methods, statistical analyzes, population characteristics and diagnostic tools across different cultures and research settings and would make comparison between different studies and across countries difficult (1, 10). Because of the high prevalence of COPD worldwide, it has been increasing focus on different preventable or modifiable risk factors for the disease. Physical comorbidity and unfavorable health behavior such including smoking and lifestyle are examples of such risk factors.

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is the fourth most common cause of death worldwide (1). About 90% of deaths caused by COPD are located in low- and middle-income countries. The gender difference in COPD prevalence is decreasing, caused by increased smoking among women in high-income countries (3).

To diagnose COPD, a lung function test, spirometry, is conducted. Spirometry is a valid test for diagnosing COPD (2, 24, 25). The test measures how an individual inhales or exhales volumes of air as a function of time, and it is usually carried out at a doctor's office or at a hospital (lung clinic) (24). The test is done by a breathing tube being placed in the patients' mouth. The patient takes a complete maximal inhalation before he is told to blast the air from the lungs and continue complete exhalation until the end of test. A more thorough explanation of the spirometry examination in this study is given in the method chapter.

The results from the spirometry serve as an objective measurement of respiratory airflow. A spirometry test provides many different values reflecting different aspects of lung function. To diagnose COPD, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and percent predicted forced expiratory volume in 1 second (pp FEV_1) are the most commonly used markers. Common criteria for COPD are set by GOLD and are based on a FEV_1/FVC ratio less than 70% (1, 25). The severity of COPD should be graded by ppFEV1 and categorized according to the GOLD guidelines. Recently, new Norwegian reference equations for lung parameters in the population were established in the Nord-Trøndelag Health Study (HUNT 2, 1995-1997) (26). HUNT is a large cohort study of 65,000 adults (27, 28).

Anxiety and depression are two of the most prevalent mental health conditions in adults (29). Key features of depression are lowered mood, anhedonia, feelings of guilt, poor motivation and low self-esteem. In addition, a wide spectrum of physical and functional symptoms, like sleep, appetite disturbance and lack of energy, are prominent (8, 30). Main features of anxiety are feeling of fear, worrying and worst case scenario-thinking. Somatic symptoms of anxiety are nervousness, tremor, sweating, tachycardia, dizziness and tachypnea among others (30).

In a large cross-sectional study, the European Study of the Epidemiology of Mental Disorders (ESEMeD), by Alonso et al. (n=21,425), they found a lifetime prevalence of any anxiety disorder to be 13.6% in general population (31). In the same study, lifetime prevalence of any mood disorder in the general population was estimated to be 14.0%. The 12-month prevalence for any anxiety and any mood disorder was 6.4 % and 4.2%, respectively.

Diagnosing anxiety and depressive disorders is most often done by a psychiatrist or a clinical psychologist. However, in epidemiological studies, due to large sample sizes, the use of validated self-report questionnaires is the most common method to assess mental health symptoms and behaviors. Many different questionnaires are used for these purposes. Hamilton Anxiety Rating Scale (32), Beck Anxiety Inventory (33) and State-Trait Anxiety Inventory (34) are examples on questionnaires that exclusively measures anxiety symptoms. Questionnaires like Hospital Anxiety and Depression Scale (35), Hopkins Symptom Check List (36) and Patient Health Questionnaire (37) cover both anxiety and depression, and provide sub scores for anxiety, depression and a total score for mixed anxiety and depression symptoms.

Symptoms of anxiety and depression have shown great overlap with COPD (5, 8, 11, 12), and overall the overlap seem to increase with severity of COPD (10). A review by Mikkelsen et al. (9) reveals a significant overrepresentation of anxiety and depression in people with COPD, in terms of both self-reported symptoms and psychiatric diagnosis. Factors associated with anxiety and depression in COPD are: physical disability, low body mass index, severe dyspnea, poor quality of life, female gender, presence of comorbid physical illnesses and predicted $FEV_1 < 50\%$ among others (10).

Symptoms of anxiety and depression have an additional negative impact on quality of life in people with COPD, resulting in increased mortality risk, length of stay in hospital, overall symptom burden, greater disability and impaired functional status (5).

Prevalence of self-reported symptoms of depression in people with COPD, measured by HADS-D at a cut off of 8 has been reported to be between 20 and 28 % (38, 39). In contrast to this, a study by Engström et al. found a prevalence of 7 %, yet this study had a higher cut off value of depression of HADS, at 10 points (12). Further, depression is known to be one of the main determinants of impaired quality of life in COPD (12). Importantly, though, the depressive syndrome (both self-reported and diagnosed) includes a variety of somatic symptoms (40). This brings challenges to separating whether these somatic symptoms are a part of the depressive spectrum or rather secondary, caused by somatic illness. The prevalence of symptoms of anxiety among people with COPD, measured by HADS, is reported to be higher than estimates for depression. Dowson et al. reported that 50 % of COPD inpatients had clinically significant anxiety (39) and this is similar to other studies included in a review done by Hynninen et al. (4). In another study, the prevalence of symptoms of anxiety was found to be 13 % (12).

Despite the fact that some studies point out the high prevalence of self-reported symptoms of anxiety and depression among people with COPD (38, 39), Engström et al. did not find any significant differences in anxiety nor depression between people with COPD and those with normal lung function (12).

Both biological and behavioral mechanisms seem to link COPD with increased levels of anxiety and depression. Breathing is biologically regulated by neural networks in the brainstem, mainly in the Medulla Oblongata (41). Respiration is also controlled by metabolic demands and decreased oxygen saturation in the blood, which may cause neuronal damage if not compensated (42). Dyspnea, common among people with heart- and lung diseases, is

known to be a trigger for anxiety among other conditions, causing a feeling of suffocation (2, 43). Reversely, the autonomic response of breathing is also constantly responding to changes in emotions such as happiness, fear and anxiety (44). Changes in respiration patterns due to changes in emotions are regulated by the Amygdala, a part of the reptile brain that has a crucial role in processing negative emotions such as fear and anxiety (41, 44). A complex interaction between the limbic system (including Amygdala), the cortical structures and Medulla Oblongata influences respiration (44).

Living with a chronic illness like COPD may lead to feelings of frustration, helplessness and hopelessness (45), which are common symptoms in anxiety and depression. Also, having COPD is associated with poorer global health, reduced physical activity and impaired social functioning. All these factors are also well established risk factors for anxiety and depression. Hypoxia (caused by COPD and smoking), smoking, exacerbation of COPD and untreated chronic depression may all lead to comorbid depression among people with COPD (8, 9).

Depression is closely linked to smoking (46). Also here, the direction of the association is bidirectional (47). Nevertheless it contributes negatively to the COPD - depression linkage. Because of the widespread prevalence of symptoms of anxiety and depression it is interesting to investigate this in a large population study like HUNT 2. By doing a cross-sectional study of these associations, however, we will not be able to say anything of the direction of causality. Still, we can estimate the prevalence of anxiety and depression symptoms and maybe draw some conclusions towards the need of more adequate treatment of these symptoms in people with COPD.

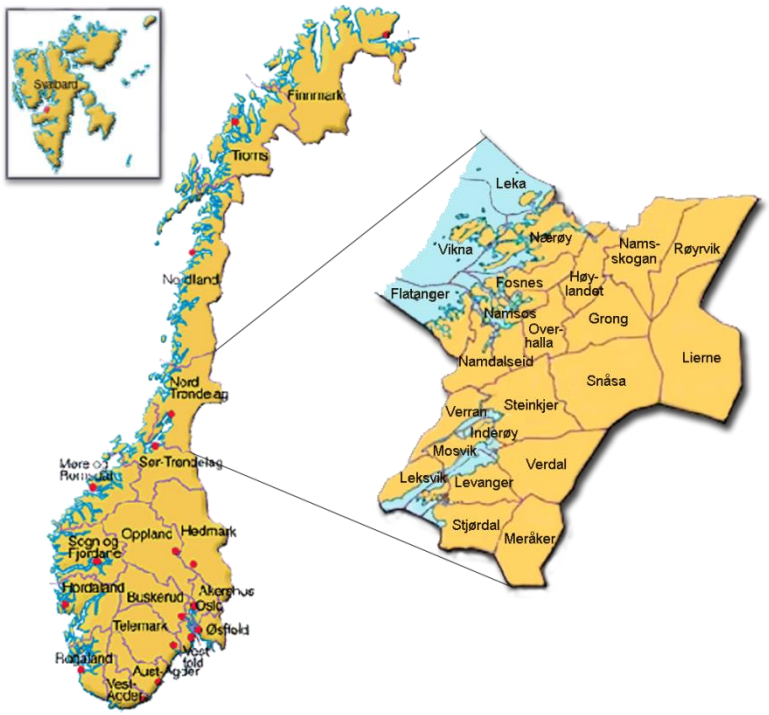
The importance of looking at associations between COPD and symptoms of anxiety, depression and mixed symptoms is among many reasons to find areas where different guidelines for treatment are needed.

Materials and methods

Study population and area

The second wave of the Nord-Trøndelag Health Study (HUNT 2, 1995-97) is a large-scale population survey where all resident of Nord-Trøndelag County, aged 20 years and older, were invited (28). Nord-Trøndelag County (Figure 1) is in the middle of Norway and is sparsely populated with a stable and homogenous population of 127,000 (1995). Nord-Trøndelag County is very suitable for epidemiological studies, having less than 0.3 % migration per year and less than 3 % non-Caucasian.

Figure 1 Norway and Nord-Trøndelag County



HUNT 2 is a follow-up study of HUNT 1 conducted in 1984-1986. HUNT 2 had bold focus on public health problems like cardiovascular disease, diabetes, obstructive lung disease and mental health among others (27).

93.898 inhabitants of Nord-Trøndelag County were invited and eligible to participate in HUNT 2. The written invitation included a questionnaire (http://www.ntnu.no/c/document_library/get_file?uuid=c6786f4d-6175-459c-a80a-5d4268cc166e&groupId=10304) addressing demographic data, life style, physical and mental health factors including the Hospital Anxiety and Depression Scale (HADS) (48).

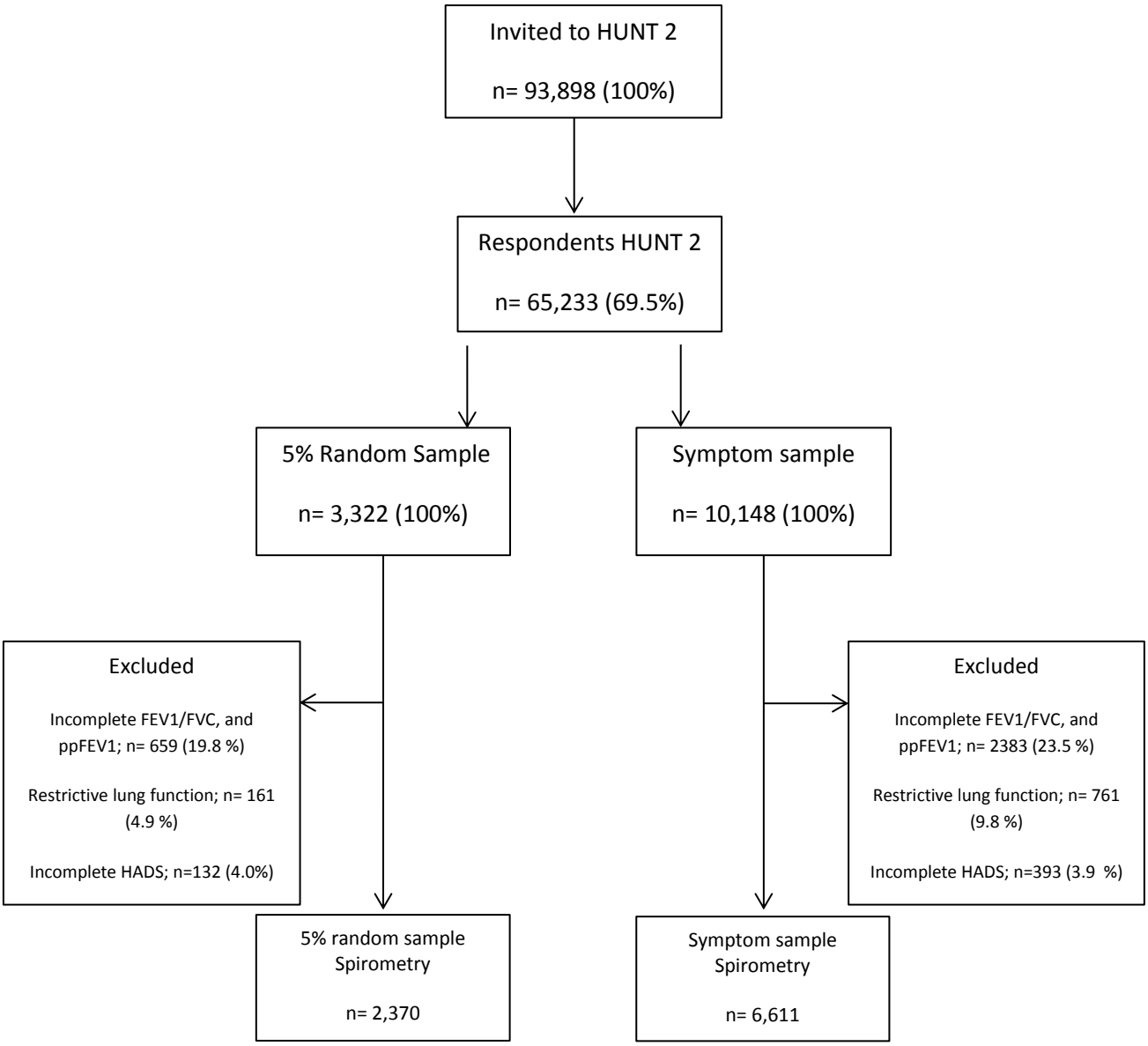
The questionnaire was to be filled out prior to the screening and brought to the screening site were additional physical examination were conducted. These examinations were measurements of blood pressure, heart rate, height, weight, waist and hip circumferences and additional clinical measurements in sub-samples like lung function, bone densitometry, hearing, vision, headache/migraine, ankle blood pressure and sensibility in the foot (27).

Compared to other population studies, HUNT 2 has several advantages such as covering a total population within a geographical area, wide age range (20 year and older) and a relatively high participation rate, 69,5 % (27).

A study population of a total 65, 233 (69.5 % of invited) attended HUNT 2. Of these a respiratory symptom sample (n= 10,148) and a random 5% sample (n=3,322) attended the HUNT Lung study (26). This selection was done due to limited capacity for spirometric measurements at the screening stations. To be included in the respiratory symptom sample the participants must have answered "yes" to any of the following questions: "Do you have or have you had asthma?", "Do you use or have you used asthma medications?" and "Have you had attack of wheezing or breathlessness during the last 12 months?" None of the participants in the symptom sample were included in the random sample (17).

Of the 10,148 participant in the symptom sample, 3,537 were excluded due to incomplete values of spirometry, possible restrictive lung function or incomplete HADS responds (see Figure 2). Of the included people in the random sample, 952 participants were excluded from the study by the same criteria, leaving us with a symptom sample of 6,611 and a random sample of 2,370.

Figure 2
Float scheme for inclusions criteria



Study design

The study was conducted as a descriptive, cross-sectional study. Cross-sectional study design was chosen because it is suitable for studying large populations and is known for its efficiency (49, 50). Cross-sectional studies are inexpensive and relatively easy to conduct. The design is also fit to measure prevalence of different factors within a population. The method is also suitable for identifying associations between disorders. Findings from cross-sectional surveys can be generalized to the base population, and to some extent, to other similar populations. On the other hand there are limitations using this kind of method, because it can only give clues about etiology. Because exposure and outcome are measured simultaneously one can never be sure, in the presence of an association, which is the cause and which is the consequence (51).

Measurements

Dependent variable – anxiety and depression

To address symptoms of anxiety and depression in HUNT 2, the Hospital Anxiety and Depression Scale (HADS) was included as a part of questionnaire 1 in HUNT 2. The HADS is a widely used questionnaire and has been thoroughly validated for use among inpatients in both psychiatric and somatic institutions, in primary care settings and in the general population (52, 53). It consist of seven items for depression (HADS-D) and seven for anxiety (HADS-A).

Each item has a four-point ordinal scale to describe symptom severity from zero to three (48). The score for each subscale ranges from 0-21. 0-7 indicates normal state, 8-10 borderline state, and 11-21 anxiety or depression state. If one or two answers were missing, we extrapolated the total score by multiplying the sum by 7/5 or 7/6. Anxiety or depression was categorized as HADS-A or HADS-D score of 8-21, where 0-7 was no anxiety or no depression. Mixed anxiety and depression was defined by cases with both HADS-A and HADS-D 8-21.The psychometric properties of the Norwegian version of the HADS have found to be excellent in HUNT 2 (53).

The dependent variables were dichotomized. We took the HADS categorical variable, where “0= no anxiety or depression”, “1=pure anxiety”, “2=pure depression”, and “3=mixed anxiety and depression “. We then extracted pure anxiety, and dichotomized it into “No anxiety or depression = 0”, and “Pure anxiety =1”. The same was done to pure depression and mixed symptoms. No anxiety or depression had always the value “0”.

Independent variables – Lung function

Lung function can be measured in several ways (2), but to do a spirometry is common. In HUNT 2 lung function was recorded using pneumotachographs (MasterScope spirometer, version 4.15, Erich Jaeger GmbH, Wuerzburg, Germany) (26). A pneumotachograph measures flow and integrates it into volume which gives us a flow/volume curve.

To conduct spirometry examinations in HUNT 2, 19 nurses and technicians were organized into two teams. Team one covered the 5 most inhabited municipalities and team two covered the 18 smaller municipalities (26). The staff was trained to instruct the participants to perform three acceptable spirometries, ensuring that the participants produced the highest possible peak flows and that expiration continued for six seconds or more. The flow/volume curve with the highest values of FEV_1 and FVC was retained. The participants were seated and wore a nose clip during session. Extension or flexion of the neck was avoided. Further description of the spirometry in HUNT 2, is explained elsewhere (26).

Using spirometry we measured the Forced Expiratory Volume in 1 second (FEV_1) and the Forced Vital Capacity (FVC). The values of FEV_1 and FVC are important indicators for lung function, including diagnosing COPD (2).

Forced Expiratory Volume in 1 second (FEV_1) is reproducible. Since the forced expiratory volume is independent of effort, this explains a constant value despite repeatedly measurements as long the individual maintains the same lung function. Forced Vital Capacity (FVC) is not as equally reproducible as FEV_1. FVC and FEV_1 are dependable of gender, age, height and ethnicity (2).

We included all subjects with baseline spirometry, FEV_1, FVC and ppFEV, and who had answered the HADS questions from the Lung study and that were present in the symptom or random selection in our study (Figure 2). Local prediction equations for percent predicted forced expiratory volume in one second ($ppFEV_1$) were used (26).

Lung function was defined by forced expiratory volume in one second percentage predicted ($ppFEV_1$) and categorized as followed; $\geq$100.0, 80.0-99.9, 50.0-79.9, and <50.0.

COPD was defined according to GOLD classification (1), with a FEV_1/FVC ratio <0.70 and $ppFEV_1 \geq$ 80 (stage 1), $ppFEV_1$ =>50-80, and $ppFEV_1$ <50. Normal lung function was defined with FEV_1/FVC >0.70 and $ppFEV_1$ >80. Participants with lung function FEV_1/FVC <0.70 and ppFEV1 > 80 was defined as restrictive and excluded from our study population.

To obtain statistical power we merged COPD stage 3 (severe COPD) and stage 4 (very severe COPD). The COPD- variable was used as a categorical variable in our bivariate and multivariate regression analyzes.

Demographic variables

Age, gender, cohabitant status, education and work status were used as demographic variables. Cohabitant status was dichotomized as living alone (0) or not (1). Education was categorized according to the Norwegian education system and was transformed into more (1) or less (0) than 9 years of education. Working status was constructed by those who answered "yes" to work, self-employed, military service or education (1) and those answering "yes" to unemployed, retired, social welfare (0).

Life style factors

Smoking, physical activity, and Body Mass Index (BMI) was included as life style factors. Smoking was categorizes as current, former and never smoker. Later it was dichotomized as non-smoker (0) and current or former smoker (1). Physically activity was dichotomized into physically active "yes" (1) or "no" (0). BMI was obtained as a continuous variable.

Somatic diseases

Positive answers to "have you or have you ever had…" – heart attack, angina pectoris, diabetes, cancer, stroke, or other chronic disease was dichotomized as Chronic somatic disease "yes" (1) or "no" (0).

Ethics

Each participant in HUNT 2 confirmed their participation with a written consent which was legit to the screening, subsequent control and follow-up. Each participant also approved for their data and blood samples to be used for research (27). They were able to withdraw their consent from the study at any time.

The Norwegian Data Inspectorate, the Regional Committee for Ethics in Medical Research and the HUNT publication Review Board approved the protocols for HUNT 2. This study is also approved by The Regional Committee for Ethics in Medical Research and The Hunt publication Review Board (Appendices 1 and 2).

Statistical analyses

This study aims to investigate the associations between lung function and HADS, with focus on COPD and pure depression, pure anxiety and mixed depression and anxiety.

We used chi-square test and t-test to make a descriptive presentation of our data. This presentation of demographic, lifestyle, comorbidity and psychiatry data in the study is shown in Table 1. Further, we performed a bivariate regression, with dichotomized HADS variables as dependent variable and lung function as independent variable, to compute crude odds ratios (OR) and 95% confidence intervals (CI). A logistic multivariate regression analyze was then conducted, with HADS as dichotomized variables and COPD as categorical variables. Demographical, life style factors and somatic disease were adjusting variables. In this analysis we estimated adjusted ORs for subtypes of anxiety and depression according to lung function and 95% confidence intervals for the same groups. We adjusted for age, sex, physical activity, smoking habit, cohabitant and chronic diseases. In a further analysis, we stratified by gender.

Cross tables stratified on gender and age, to make a better overview of our data, are presented separately (Appendices 3 and 4).

P-value <0.05 was defined as statistical significant. The IBM SPSS statistics for Windows was our analysis tool (54). We decided not to weigh our sample or to do a trend test for this thesis.

Results

Table 1 gives a descriptive presentation of the two groups selected for this study; the lung symptom group (Symptom group, n= 6,611) and the randomly selected group (Random group, n=2,370).The symptom group had a somewhat higher proportion of males (48.3% vs. 46.3) and mean age was marginally higher (50 vs. 49 years). Participants in the symptom group were more likely to be unemployed, have less education, and more likely to be living alone then participants in the random group.

Concerning life style factors included in this study, more people in the symptom group were current smokers, 35.9% vs. 28.9%. More participants in the random group were physically active and they had a slightly lower Body Mass Index than the symptom group.

In our descriptive presentation (Table 1), The Mean HADS total score of depression was 4.1 (SD 3.4) for our symptom sample and 3.3 (SD 3.0) for our random sample. Stratifying by gender the HADS-Depression score among men was higher than for women; 4.0 (SD 3.3) and 3.7 (SD 3.3), respectively. This supports the results from our cross tables that men reported depression more frequent than women.

Further, symptoms of pure anxiety, pure depression and mixed anxiety and depression were all more commonly reported in the symptom group than in the random group. Also, as expected, abnormal lung function measures (spirometry) were more frequent in the symptom group then in the random group (moderate COPD: 16.6% vs. 6.9%).

Because of this considerable overlap between the two study groups in terms of reduced lung function, we chose to merge the two groups and then divide into conventional classification of lung function (GOLD-classification) for the further analyses.

Table 1
Descriptive presentation of symptom group and random group

	Symptom (% or SD)	Random (% or SD)	p-value
Participants (symptom/random)			
Demographic			
Male sex (6611/2370)	3196 (48.3)	1097 (46.3)	0.085
Age (6611/2370)	49.8 (16.7)	48.9 (15.9)	0.031
Cohabitant (5036/1851)	4273 (84.8)	1623 (87.7)	0.003
Employed (6521/2340)	4108 (63.0)	1669 (71.3)	<0.001
Education (6380/2295)			
- <= 9 years	2472 (38.7)	776 (33.8)	<0.001
- > 9 years	3908 (61.3)	1519 (66.2)	<0.001
Lifestyle			
Body Mass Index (6972/2470)	26.9 (4.4)	26.2 (3.8)	<0.001
Smoking (6522/2333)			<0.001
- Never smoker	2250 (34.5)	1011 (43.3)	
- Former smoker	1928 (29.6)	647 (27.7)	
- Current smoker	2344 (35.9)	675 (28.9)	
Physical activity (5050/1850)			<0.001
- Inactive	2353 (46.6)	762 (41.2)	
- Moderate	2450 (48.5)	988 (53.4)	
- Physical active	247 (4.9)	100 (5.4)	
Somatic disorders[a)]			
One or more chronic disease	1628 (24.6)	398 (16.8)	<0.001
Hospital Anxiety and Depression Scale			
HADS categories[b)] (6611/2370)			<0.001
- No anxiety or depression	4354 (65.9)	1824 (77.0)	
- Pure anxiety	1215 (18.4)	305 (12.9)	
- Pure depression	349 (5.3)	82 (3.5)	
- Mixed anxiety and depression	693 (10.5)	159 (6.7)	
Mean HADS sum total score			
- Anxiety (6445/2248)	6.0 (3.7)	5.1 (3.2)	<0.001
- Depression (7197/2476)	4.1 (3.4)	3.3 (3.0)	<0.001
Lung function			
ppFEV1[c)] (6611/2370)			<0.001
- =>100.0	1930 (29.2)	1030 (43.5)	
- 80.0 – 99.9	3219 (48.7)	1153 (48.6)	
- 50.0 – 79.9	1095 (16.6)	163 (6.9)	
- <50.0	367 (5.6)	24 (1.0)	
COPD[d)] severity (6611/2370)			0.001
- No COPD	4719 (71.4)	2058 (86.8)	
- Mild	430 (6.5)	125 (5.3)	
- Moderate	1095 (16.6)	163 (6.9)	
- Severe	367 (5.6)	24 (1.0)	

a) Dichotomized answer "yes" to have you ever had or do you have Heart attack, Angina Pectoris, Diabetes, Cancer, Stroke and other chronic somatic disorder
b) A score $\geq$ 8 for symptoms of anxiety and/or depression in HADS was dichotomized into "No anxiety or depression", "Pure anxiety", "Pure depression" or "Mixed anxiety and depression"
c) $ppFEV_1$ percent predicted forced expiratory volume in one second
d) According to GOLD-classifications (see method)

Table 2 presents crude and adjusted odds ratios (OR) for symptoms of pure anxiety, pure depression and mixed anxiety and depression above cut-off levels, in association with lung function. Lung function is defined according to GOLD classification (see Methods); here after referred to as mild COPD, moderate COPD or severe COPD. Those with normal lung function represented the reference group in this study.

Crude associations of symptoms of pure anxiety weakened with decreasing lung function, yet this was explained by differences in age and gender distribution. Further adjustment did not alter these results.

In the crude analysis there was a 3-fold increased odd for pure depression in the group for severe COPD, but this effect was attenuated with further adjustment, and towards the null in Model 3. In the fully adjusted model, the following covariates influenced the association between COPD and pure depression the most; male gender (OR 1.98 and 95% CI 1.44-2.70), age (OR 1.04 and 95% CI 1.03-1.06) and education > 9 yrs. (OR 1.35 and 95% CI 0.99-1.83). In contrast, living in a relationship (OR (CI): 0.51 (0.35-0.76) and physical activity (OR 0.57 and 95% CI (0.42-0.75), were protective factors in the association between COPD and pure depression.

In contrast to symptoms of anxiety, there was a tendency of increasing ORs for depression with decreasing lung function. Of note, no statistical test was run to test this trend in the current study.

The pattern was similar for symptoms of mixed anxiety and depression, yet the ORs were smaller and less robust for adjustment; unadjusted excess risk in the COPD 3 group was 50% higher than in the reference group, but was non-existing in Model 2.

Table 2

Crude and adjusted ORs for pure anxiety, pure depression and mixed anxiety and depression symptoms[a] in association with lung function

Exposure	Pure anxiety OR (CI)	p-value	Pure depression OR (CI)	p-value	Mixed anxiety and depression OR (CI	p-value
Lung function						
- Mild COPD	0.88 (0.69-1.12)	0.289	1.55 (1.06-2.26)	0.022	1.15 (0.86-1.54)	0.361
- Moderate COPD	0.90 (0.76-1.07)	0.217	1.91 (1.49-2.46)	<0.001	1.34 (1.10-1.63)	0.004
- Severe COPD	0.70 (0.51-0.97)	0.034	3.28 (2.34-4.60)	<0.001	1.52 (1.11-2.09)	0.009
Model 1[b]						
Lung function						
- Mild COPD	1.04 (0.81-1.33)	0.763	0.98 (0.66-1.44)	0.906	1.06 (0.79-1.43)	0.706
- Moderate COPD	1.12 (0.94-1.34)	0.219	1.02 (0.78-1.33)	0.910	1.17 (0.95-1.44)	0.144
- Severe COPD	0.97 (0.69-1.35)	0.852	1.40 (0.98-2.02)	0.065	1.26 (0.90-1.75)	0.176
Model 2[c]						
Lung function						
- Mild COPD	0.98 (0.736-1.31)	0.896	0.77 (0.47-1.29)	0.326	0.996 (0.69-1.43)	0.983
- Moderate COPD	1.07 (0.866-1.33)	0.515	1.06 (0.76-1.48)	0.752	1.01 (0.77-1.32)	0.963
- Severe COPD	0.74 (0.504-1.19)	0.241	1.28 (0.80-2.03)	0.301	0.76 (0.47-1.23)	0.264
Model 3[d]						
Lung function						
- Mild COPD	1.09 (0.78-1.46)	0.679	0.86 (0.49-1.49)	0.580	0.90 (0.58-1.39)	0.895
- Moderate COPD	1.15 (0.88-1.45)	0.332	0.95 (0.63-1.42)	0.796	0.80 (0.57-1.12)	0.798
- Severe COPD	1.17 (0.67-1.81)	0.694	1.01 (0.51-1.89)	0.968	0.66 (0.34-1.28)	0.657

a) Cut off for pure anxiety, pure depression and mixed anxiety and depression was ≥ 8
b) Adjusted for gender and age
c) Adjusted for cohabitant, work status and education
d) Adjusted for physical activity, body mass index (BMI), somatic diseases (Heart attack, Angina Pectoris, Diabetes, Cancer, Stroke and other chronic somatic disorder) and smoking

Given the results for pure depression, we next performed the same logistic regression analysis stratified by gender (Table 3). In male participants, the crude OR for symptoms of pure anxiety decreased as lung function deteriorated. After adjusting for age, this pattern changed, and in Model 3 men with severe COPD had almost 60 % higher OR for symptoms of pure anxiety than those with normal lung function. Still, statistical evidence for this finding is at borderline. Females had a slight increase in OR of pure anxiety from mild COPD to moderate COPD, and then a decrease from moderate COPD to severe COPD. The tendency remained the same for Model 1, Model 2 and Model 3 for females.

In males, unadjusted logistic regression showed an increase in OR for pure depression with decreasing lung function. This effect was attenuated beyond statistical significance in the further steps of adjustment. For women, there was a significant increase in crude OR for symptoms of pure depression for all three stages of COPD. In Model 1, the OR for women with severe COPD was reduced by 50%. A two-fold increased OR for pure depression remained robust to further adjustments in females. Although statistic evidence is weak, the point estimates (ORs) indicate that the association with depression is stronger in females than males.

In the crude logistic regression on symptoms of mixed anxiety and depression, men had an increased OR in mild and moderate COPD, and decrease in OR for moderate to severe COPD. This pattern remained throughout the fully adjusted model, and ORs generally decreased with adjustment. In Model 3 men with moderate COPD had a reduced OR (0.61 and 95% CI 0.37-1.00). Women with moderate, OR (1.59 and 95% CI 1.20-2.09) and severe, OR (2.35 and 95% CI 1.51-3.65) COPD had a significant increase of mixed symptoms in the crude analysis. After adjustment for age there was still an increase in line with exacerbated lung function, but only statistically significant for those with severe COPD, OR (1.75 and 95% CI 1.12-2.76).

Table 3

Crude and adjusted ORs for pure anxiety, pure depression and mixed anxiety and depression symptoms[a] in association with lung function, stratified by gender

Exposure	Pure Anxiety OR (CI)	p-value	Pure Depression OR (CI)	p-value	Mixed anxiety and depression OR (CI)	P-value
Lung function						
Female						
COPD 1 (mild)	0.98 (0.69-1.39)	0.913	2.07 (1.14-3.77)	0.017	1.31 (0.86-2.00)	0.215
COPD 2 (moderate)	1.09 (0.87-1.37)	0.462	2.00 (1.30-3.08)	0.002	1.59 (1.20-2.09)	0.001
COPD 3 (severe)	0.81 (0.50-1.32)	0.396	3.59 (1.94-6.64)	<0.001	2.35 (1.51-3.65)	<0.001
Male						
COPD 1 (mild)	0.88 (0.62-1.25)	0.485	1.20 (0.74-1.95)	0.463	1.08 (0.72-1.62)	0.723
COPD 2 (moderate)	0.82 (0.63-1.05)	0.116	1.69 (1.24-2.30)	0.001	1.20 (0.90-1.59)	0.209
COPD 3 (severe)	0.73 (0.47-1.13)	0.156	2.78 (1.85-4.18)	<0.001	1.10 (0.68-1.79)	0.704
Model 1[b]						
Lung function						
Female						
COPD 1 (mild)	1.01 (0.72-1.44)	0.941	1.34 (0.72-2.48)	0.356	1.11 (0.72-1.71)	0.642
COPD 2 (moderate)	1.15 (0.90-1.45)	0.268	1.15 (0.73-1.80)	0.556	1.28 (0.96-1.71)	0.092
COPD 3 (severe)	0.87 (0.53-1.41)	0.561	1.78 (0.94-3.35)	0.076	1.76 (1.12-2.76)	0.015
Male						
COPD 1 (mild)	1.12 (0.76-1.07)	0.537	0.82 (0.50-1.35)	0.433	1.02 (0.67-1.54)	0.925
COPD 2 (moderate)	1.18 (0.90-1.55)	0.243	0.97 (0.69-1.35)	0.838	1.10 (0.81-1.50)	0.525
COPD 3 (severe)	1.27 (0.80-2.02)	0.318	1.30 (0.84-2.02)	0.238	0.98 (0.59-1.61)	0.923
Model 2[c]						
Lung function						
Female						
COPD 1 (mild)	0.96 (0.63-1.44)	0.824	0.71 (0.45-2.01)	0.516	1.16 (0.69-1.98)	0.573
COPD 2 (moderate)	0.99 (0.73-1.32)	0.917	1.13 (0.63-2.04)	0.684	1.13 (0.78-1.63)	0.534
COPD 3 (severe)	0.61 (031-1.19)	0.149	1.90 (0.64-1.94)	0.128	1.37 (0.69-1.98)	0.324
Male						
COPD 1 (mild)	1.06 (0.70-1.59)	0.917	0.79 (0.44-1.41)	0.423	0.87 (0.53-1.44)	0.588
COPD 2 (moderate)	1.29 (094-1.77)	0.121	1.03 (0.68-1.54)	0.904	0.93 (0.64-1.37)	0.717
COPD 3 (severe)	1.14 (0.64-2.01)	0.662	1.12 (0.64-1.94)	0.696	0.43 (0.19-0.96)	0.038
Model 3[d]						
Lung function						
Female						
COPD 1 (mild)	0.99 (0.63-1.59)	0.988	0.91 (0.31-2.67)	0.858	1.13 (0.61-2.13)	0.691
COPD 2 (moderate)	1.11 (0.79-1.58)	0.545	0.88 (0.39-2.00)	0.760	1.07 (0.67-1.72)	0.767
COPD 3 (severe)	0.93 (0.45-2.40)	0.930	2.46 (0.74-8.13)	0.141	1.87 (0.76-4.65)	0.176
Male						
COPD 1 (mild)	1.19 (0.78-1.07)	0.423	0.84 (0.44-1.61)	0.605	0.77 (0.41-1.45)	0.363
COPD 2 (moderate)	1.27 (0.88-1.83)	0.195	0.99 (0.62-1.58)	0.963	0.61 (0.37-1.00)	0.052
COPD 3 (severe)	1.57 (0.84-2.96)	0.160	0.82 (0.38-1.76)	0.604	0.38 (0.13-1.10)	0.074

a) Cut off for pure anxiety, pure depression and mixed anxiety and depression was ≥ 8
b) Adjusted for age
c) Adjusted for a + cohabitant, education and work status
d) Adjusted for a+ b+BMI, physical activity, smoking and somatic diseases (Heart attack, Angina Pectoris, Diabetes, Cancer, Stroke and other chronic somatic disorder)

Appendices 3a and b present cross tables for HADS categories by COPD class, stratified by gender and age under or above 50 years, to help give a more detailed overview of the distribution of subtypes of anxiety and depression depending on lung function in the study sample. Of note, low numbers of COPD cases under the age of 50 years make firm

Discussion

This population based study indicates gender specific associations of symptoms of anxiety and depression with lung function. The prevalence of depression was higher in males than females in our total sample, but only women had increased odds for depression and mixed anxiety and depression attributed to decreased lung function. Inversely, our results indicate that only men report higher rates of pure anxiety in severe COPD. Statistical evidence was, however, borderline. Findings regarding depression in COPD are in keeping with literature, yet the observed increased risk for anxiety in males with severe COPD contradicts earlier findings (4, 8, 14, 55).

Gender differences in anxiety and depression in the general population

In general, depression is thought to be more common among women (13). There might be different reasons for this; women might actually be more vulnerable to depression, but they are also more likely to admit and acknowledge depressive symptoms and seek help than men (56). In contrast, however, women reported depression less frequent than men. This may be caused by the properties of HADS and the sampling procedures in this study. This scale focuses mainly on anhedonia in depression, which has proven to be a gender neutral depressive symptom (57).Of note; Stordal et al. (58) found no differences between the genders in their study of the total HUNT 2 population. Further, one of the purposes for the HADS scale is to exclude the somatic symptoms of anxiety and depression among physically ill people. It is known that women more often report somatic symptoms of depression than men, and in sum these factors may explain the observed gender patterns described above.

Some studies report that depression increase with age, yet findings are still conflicting (59, 60). Stordal et al. (59), found a close to linear increase in depression symptoms with age in both genders. In a further study, the same authors found that somatic symptoms and diagnoses explained most of the association between depression and age (61). These studies were conducted in the same population as the present study. In our study depression symptoms increased with 4% per year of age. This close relationship was illustrated by the marked drop

in OR after age adjustment in our logistic regression analysis (Table 2). Of note, the close association of HADS-Depression score with age have been observed in previous population based studies using the HADS scale, and might be explained by anhedonia, which is one of main symptoms of depression and tend to increase with age (59, 62).

Gender specific associations between symptoms of anxiety and depression and COPD

The findings for symptoms of depression in our study are consistent with a review by Hill et al. (8), where they found that more severe COPD usually correlates with higher depression score on screening instruments. A gender specific finding, showing that women had higher odds for depression with decreasing lung function is also documented in earlier studies (13, 14, 55). As observed in most previous studies of patient samples and in the general population, women with COPD seemed to be more exposed to depression symptoms than men with the same condition in our study. In a study by Di Marco et al (14), females had higher levels of anxiety and depression, and also reported higher level of dyspnea which correlated with depression. Dyspnea is thought to be associated with anxiety, and within the lung symptom sample in HUNT Leivseth et al. (17) reported that people with anxiety symptoms reported more dyspnea than people without anxiety. Overall, studies report that depression in association with COPD has a larger impact on women than men in regards to quality of life and feeling of dyspnea (55, 63).

Another explanation for elevated depression scores in poor lung function might be the fact that people with severe COPD often use large doses of steroids for short periods of time, or low doses for long periods of time, both well-known risk factors for depression (64). However, to our best knowledge no studies have examined gender differences in depression caused by steroid treatment in COPD. We had no data on use of medications in our study and we were therefore not able to investigate these issues further.

Symptoms of comorbid depression in patients with COPD are associated with poorer survival, longer hospitalization, persistent smoking, increased symptom burden and poorer physical and social function. Interventions that reduce depressive symptoms may potentially affect COPD outcomes (11). According to Hynninen et al. (63), cognitive behavioral therapy (CBT) improves symptoms of anxiety and depression in patients of both genders with COPD. Of note, women had higher symptom levels of anxiety and depression than men throughout their study. In the present study, associations of symptoms of pure anxiety weakened with exacerbating lung function. This was explained by gender and age in our logistic regression

analyses (Table 2). These findings are in accordance to Engström et al. (12), who found a somewhat higher percentage of anxiety among patients with COPD, but it was not statistically significant.

The earlier mentioned review by Hynninen et al. (4) includes 19 studies of anxiety in COPD patients. Four of these studies used HADS, and found a prevalence of anxiety between 13%-57%. These numbers are similar to the prevalence of symptoms of pure anxiety in our study. It is difficult to compare our results directly to these findings since none of the studies included in the report by Hynninen et al. had more than 141 participants, and more than 50% of the participant had to be diagnosed with COPD. Our study has a far larger sample and there are reasons to believe that we also investigated participants in a stable period of their COPD, and our selection was not based on a COPD diagnose.

Laurin et al. (55), who investigated psychiatric disorder among COPD outpatients in a stable phase found a higher rate of anxiety than depression in their study. They also found that women had 1.5 times the rate of anxiety disorder than men. This was opposite our findings, where no associations of anxiety with COPD severity throughout our regression analyses.

Some of the differences in results between our study and other studies might be the explained by the different instruments used to address symptoms of anxiety and depression. Some instruments exclusively measure anxiety symptoms (32-34) and others provide a sub score for anxiety-related symptoms, which makes it possible to investigate self-reported symptoms of pure anxiety (35-37). Anxiety and depressive symptom overlap greatly (53). In order to avoid misclassification between anxiety and depression, we chose to study symptoms of pure anxiety and depression as mutually exclusive symptom groups. Most previous studies using HADS and other instruments have not done this, and therefore most of them have included many participants with anxiety in their "depression group", and vice versa.

Overall, people with severe COPD, had a 52% increased odds of reporting mixed anxiety and depression symptoms, compared to those with normal lung function. Women with severe COPD had 2-fold increased odds for reporting mixed symptoms compared to men. We have not been able to find studies who investigate self-reported symptoms of mixed anxiety and depression within lung function. However, Katon et al. (65) emphasizes the importance of revealing subclinical mixed anxiety and depression in the population, because they tend to have many medical non-explained symptoms and are at risk of more severe affective and anxiety disorders when exposed to stress, i.e. physical sickness. Laurin et al (55), found a

prevalence of both current anxiety and mood disorder of 14% (n=16), but did not discuss these findings in relation to single conditions further. However, findings from their study are similar to the prevalence of symptoms of mixed anxiety and depression in the present study, ranging 6.6-16.5% for men and 7.7-19.2% for women. Das-Munshi et al. (66) found a prevalence of 8.8 % in the general population of mixed anxiety-depressive disorder (MADD), a subclinical category that do not meet the diagnostic criteria of clinical anxiety, depression or comorbid depression and anxiety disorders according to ICD-10. MADD may account for half of all cases of common mental disorder in Great Britain, and have similar impact on quality of life as anxiety and depression. It also has a negative impact upon population health and well-being. These finding strengthen the importance of revealing mixed anxiety and depression in the population.

Strengths and limitations

The current study has several strengths. The sample size is large and includes female and male participants across the whole adult lifespan. Lung function was clinically examined using spirometry as recommended by international guidelines. Further, a wide range of baseline variables known to influence both mental health and lung function for all participants was included in the study. Our data was collected using validated and well established methods for assessment of lung function and anxiety and depression. The study design is fit for investigation in large populations and for identifying associations between disorders. Findings from such study may be generalized to the base population and, to some extent, to similar population. The HADS is a reliable questionnaire because of its function of isolating psychiatric symptoms from physical symptoms (48). As far as we know, the symptoms of pure anxiety and pure depression have not earlier been similar defined in large population studies. Some limitations must be acknowledged. In HUNT 2, post-bronchodilator spirometry was conducted only for those with indication of bronchial obstruction ($FEV_1/FVC<0.75$) in pre-bronchodilator spirometry. This may probably cause some misclassification according to the COPD diagnosis and must be interpreted as a limitation. Since we used self-reported symptoms of anxiety and depression instead of clinical psychiatric diagnoses, a direct comparison with results from many of the previous studies cannot be done. However this method is common in clinical practice and in epidemiological studies.

Conclusion

Results from this study indicate a high prevalence of mental distress in severe COPD, and gender specific relationships between symptoms of anxiety and depression, and lung function; in women depression was strongly associated with exacerbated lung function, while only men reported symptoms of anxiety associated with worsened lung function. There should be a greater focus on early detection and treatment of psychological symptoms among people with COPD. The assessment can be done by self-reported questionnaires, like the HADS, as a part of COPD treatment. This is one of the first studies, in a large general population, that investigate anxiety and depression sub types. Findings must therefore be replicated before new, possible gender specific strategies can be developed and implemented.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) http://www.goldcopd.org/ (15.01.13).

2. Giæver P. Lungesykdommer. Oslo: Universitetsforl.; 2008.

3. http://www.who.int/mediacentre/factsheets/fs315/en/ (01.05.13).

4. Hynninen KM, Breitve MH, Wiborg AB, et al. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. Journal of Psychosomatic Research
2005; 59: 429-43.

5. Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. Psychosomatic medicine 2003; 65: 963-70.

6. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta psychiatrica Scandinavica Supplementum 2004: 21-7.

7. Narrow WE, Rae DS, Robins LN, et al. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry 2002; 59: 115-23.

8. Hill K, Geist R, Goldstein RS, et al. Anxiety and depression in end-stage COPD. European Respiratory Journal 2008; 31: 667-77.

9. Mikkelsen RL, Middelboe T, Pisinger C, et al. Anxiety and depression in patients with chronic obstructive pulmonary disease (COPD). A review. Nordic journal of psychiatry 2004; 58: 65-70.

10. Maurer J, Rebbapragada V, Borson S, et al. Anxiety and Depression in COPDCurrent Understanding, Unanswered Questions, and Research Needs. CHEST Journal
2008; 134: 43S-56S.

11. Ng TP, Niti M, Tan WC, et al. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007; 167: 60-7.

12. Engstrom CP, Persson LO, Larsson S, et al. Functional status and well being in chronic obstructive pulmonary disease with regard to clinical parameters and smoking: a descriptive and comparative study. Thorax 1996; 51: 825-30.

13. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. General hospital psychiatry
2007; 29: 147-55.

14. Di Marco F, Verga M, Reggente M, et al. Anxiety and depression in COPD patients: The roles of gender and disease severity. Respir Med 2006; 100: 1767-74.

15. Cleland JA, Lee AJ, Hall S. Associations of depression and anxiety with gender, age, health-related quality of life and symptoms in primary care COPD patients. Family practice 2007; 24: 217-23.

16. Wilhelm FH, Trabert W, Roth WT. Physiologic instability in panic disorder and generalized anxiety disorder. Biol Psychiatry 2001; 49: 596-605.

17. Leivseth L, Nilsen TI, Mai XM, et al. Lung function and anxiety in association with dyspnoea: the HUNT study. Respiratory medicine 2012; 106: 1148-57.

18. Stratelis G, Jakobsson P, Molstad S, et al. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J Gen Pract 2004; 54: 201-6.

19. Singer HK, Ruchinskas RA, Riley KC, et al. The Psychological Impact of End-Stage Lung Disease*. CHEST Journal 2001; 120: 1246-52.

20. Felker B, Bush KR, Harel O, et al. Added Burden of Mental Disorders on Health Status Among Patients With Chronic Obstructive Pulmonary Disease. Primary care companion to the Journal of clinical psychiatry 2010; 12.

21. Folkehelseinstituttet: www.fhi.no (20.12.12.

22. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370: 741-50.

23. Pinnock H, Thomas M, Tsiligianni I, et al. The International Primary Care Respiratory Group (IPCRG) Research Needs Statement 2010. Prim Care Respir J 2010; 19 Suppl 1: S1-20.

24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-38.

25. Price D, Crockett A, Arne M, et al. Spirometry in primary care case-identification, diagnosis and management of COPD. Prim Care Respir J 2009; 18: 216-23.

26. Langhammer A, Johnsen R, Gulsvik A, et al. Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trondelag Study. European Respiratory Journal 2001; 18: 770-9.

27. Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. Norsk epidemiologi 2003; 13: 19-32.

28. NTNU HUNT research center,: http://www.ntnu.edu/hunt/inenglish (09.03.2013).

29. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 617-27.

30. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. Geneva1992.

31. Alonso J, Angermeyer MC, Bernert S, et al. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta psychiatrica Scandinavica Supplementum 2004: 28-37.

32. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32: 50-5.

33. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56: 893-7.

34. Spielberger CD, Gorsuch RL. State-trait anxiety inventory for adults: sampler set: manual, test, scoring key. Mind Garden 1983.

35. Snaith RP, Bridge GW, Hamilton M. The Leeds scales for the self-assessment of anxiety and depression. The British journal of psychiatry : the journal of mental science 1976; 128: 156-65.

36. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974; 19: 1-15.

37. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. General hospital psychiatry 2010; 32: 345-59.

38. Bosley CM, Corden ZM, Rees PJ, et al. Psychological factors associated with use of home nebulized therapy for COPD. Eur Respir J 1996; 9: 2346-50.

39. Dowson C, Laing R, Barraclough R, et al. The use of the Hospital Anxiety and Depression Scale (HADS) in patients with chronic obstructive pulmonary disease: a pilot study. N Z Med J 2001; 114: 447-9.

40. Stage KB, Middelboe T, Stage TB, et al. Depression in COPD - management and quality of life considerations. Int J Chron Obstruct Pulmon Dis 2006; 1: 315-20.

41. Brodal P. Sentralnervesystemet. Oslo: Universitetsforl.; 2007.

42. Zhang H, Wang X, Lin J, et al. Reduced Regional Gray Matter Volume in Patients with Chronic Obstructive Pulmonary Disease: A Voxel-Based Morphometry Study. AJNR Am J Neuroradiol 2012.

43. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Arch Gen Psychiatry 1993; 50: 306-17.

44. Homma I, Masaoka Y. Breathing rhythms and emotions. Exp Physiol 2008; 93: 1011-21.

45. Armstrong CL, Morrow L, SpringerLink. Handbook of Medical Neuropsychology : Applications of Cognitive Neuroscience. New York, NY: Springer New York; 2010.

46. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. The British journal of psychiatry : the journal of mental science 2010; 196: 440-6.

47. Fergusson DM, Goodwin RD, Horwood LJ. Major depression and cigarette smoking: results of a 21-year longitudinal study. Psychol Med 2003; 33: 1357-67.

48. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361-70.

49. Portney LP, Watkins MP. Foundations of Clinical Research - Applications to Practice, 3rd. ed. Pearson Education, Inc., Upper Saddle River, New Jersey: Julie Levin Alexander; 2009.

50. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.

51. Prince M, Stewart R, Ford T, et al. Practical Psychiatric Epidemiology. New York: Oxford University Press Inc., 2003: 414.

52. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002; 52: 69-77.

53. Mykletun A, Stordal E, Dahl AA. Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. The British journal of psychiatry : the journal of mental science 2001; 179: 540-4.

54. IBM SPSS Statistics for Windows, : http://www-01.ibm.com/software/no/analytics/spss/ (09.03.2013).

55. Laurin C, Lavoie KL, Bacon SL, et al. Sex differences in the prevalence of psychiatric disorders and psychological distress in patients with COPD. Chest 2007; 132: 148-55.

56. Puri BK, Lanking PJ, Treasaden IH. Textbook of Psychiatry2002.

57. Chen L, Eaton WW, Gallo JJ, et al. Understanding the heterogeneity of depression through the triad of symptoms, course and risk factors: a longitudinal, population-based study. Journal of affective disorders 2000; 59: 1-11.

58. Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: a multivariate examination. Acta Psychiatr Scand 2003; 107: 132-41.

59. Stordal E, Bjartveit Kruger M, Dahl NH, et al. Depression in relation to age and gender in the general population: the Nord-Trondelag Health Study (HUNT). Acta Psychiatr Scand 2001; 104: 210-6.

60. Kessler RC, Birnbaum H, Bromet E, et al. Age differences in major depression: results from the National Comorbidity Survey Replication (NCS-R). Psychol Med 2010; 40: 225-37.

61. Stordal E, Bjelland I, Dahl AA, et al. Anxiety and depression in individuals with somatic health problems. The Nord-Trondelag Health Study (HUNT). Scand J Prim Health Care 2003; 21: 136-41.

62. Lisspers J, Nygren A, Söderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand 1997; 96: 281-6.

63. Hynninen MJ, Bjerke N, Pallesen S, et al. A randomized controlled trial of cognitive behavioral therapy for anxiety and depression in COPD. Respir Med 2010; 104: 986-94.

64. Gift AG, McCrone SH. Depression in patients with COPD. Heart Lung 1993; 22: 289-97.

65. Katon W, Roy-Byrne PP. Mixed anxiety and depression. J Abnorm Psychol 1991; 100: 337-45.

66. Das-Munshi J, Goldberg D, Bebbington PE, et al. Public health significance of mixed anxiety and depression: beyond current classification. The British journal of psychiatry : the journal of mental science 2008; 192: 171-7.

Appendices

Appendix 1

Cross table for women for HADS with COPD, stratified by age group <50 years>

Appendix 2

Cross table for men for HADS with COPD, stratified by age group <50 years>

Appendix 3
Cross table for women for HADS with COPD, stratified by age group <50 years>

	< 50 years					**≥ 50 years**				
	No Anxiety or depression	Pure anxiety	Pure depression	Mixed Anxiety and depression	Total	No Anxiety and depression	Pure anxiety	Pure depression	Mixed Anxiety and depression	Total
Normal lung function	1600	498	39	178	2315	941	267	68	174	1450
	69.1 %	21.5 %	1.7 %	7.7 %	100 %	64.9 %	18.4 %	4.7 %	12.0 %	100 %
COPD 1 (mild)[a]	61	23	3	9	96	88	21	10	18	137
	63.5 %	24.0 %	3.1 %	9.4 %	100 %	64.2 %	15.3 %	7.3 %	13.1 %	100 %
COPD 2 (moderate)[b]	88	27	5	19	139	244	82	23	54	403
	63.3 %	19.4 %	3.6 %	13.4 %	100 %	60.5 %	20.3 %	5.7 %	13.4 %	100 %
COPD 3 (severe)[c]	12	6	1	4	23	74	15	12	24	125
	52.2 %	26.1 %	4.3 %	17.4 %	100 %	59.2 %	12.0 %	9.6 %	19.2 %	100 %
Total	1761	554	48	210	2573	1347	385	113	270	2115
	68.4	21.5 %	1.9 %	8.2 %	100 %	63.7 %	18.2 %	5.3 %	12.8 %	100

a) Adjusted for gender and continuous age
b) Adjusted for cohabitant, work status and education
c) Adjusted for physical activity, body mass index (BMI), somatic diseases (Heart attack, Angina Pectoris, Diabetes, Cancer, Apoplexy and other chronic somatic disorder) and smoking.

Appendix 4

Cross table for men for HADS with COPD, stratified by age group <50 years>

	< 50 years					**≥ 50 years**				
	No Anxiety and depression	Pure anxiety	Pure depression	Mixed Anxiety and depression	Total	No Anxiety and depression	Pure anxiety	Pure depression	Mixed Anxiety and depression	Total
Normal lung function	1356	324	57	150	1887	814	110	99	102	1125
	71.9%	19.3 %	3.0 %	7.9 %	100 %	72.4 %	9.8 %	8.8 %	9.1 %	100 %
COPD 1 (mild)[a]	80	18	1	7	106	152	23	19	22	216
	75.5 %	17.0 %	0.9 %	6.6 %	100 %	70.4 %	10.6 %	8.8 %	10.2 %	100 %
COPD 2 (moderate)b	109	25	3	16	153	394	57	58	54	563
	71.2 %	16.3 %	2.0 %	10.5 %	100 %	70.0 %	10.1 %	10.3 %	9.6 %	100 %
COPD 3 (severe)c	8	7	0	3	18	157	17	33	18	225
	44.4 %	38.9 %	0.0 %	16.7 %	100 %	71.3 %	7.6 %	14.7 %	8.0 %	100 %
Total	1553	374	61	176	2164	1517	207	209	196	2129
	71.8	17.3 %	2.8 %	8.1 %	100 %	71.3 %	9.7 %	9.8	9.2 %	100

a) Adjusted for gender and continuous age

b) Adjusted for cohabitant, work status and education

c) Adjusted for physical activity, body mass index (BMI), somatic diseases (Heart attack, Angina Pectoris, Diabetes, Cancer, Apoplexy and other chronic somatic disorder) and smoking.