Linda Leivseth

Chronic obstructive pulmonary disease; lung function, respiratory symptoms, and mortality

The HUNT Lung Study 1995–97

Thesis for the degree of Philosophiae Doctor

Trondheim, October 2013

Norwegian University of Science and Technology
Faculty of Medicine
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To Eirik, Kristine, and Håkon

Kronisk obstruktiv lungesykdom; lungefunksjon, luftveissymptomer og dødelighet

Lungeprosjektet i Helseundersøkelsen i Nord-Trøndelag 1995-97

Kronisk obstruktiv lungesykdom (KOLS) er en underdiagnostisert sykdom med høy sykelighet og dødelighet. Symptomene inkluderer tung pust, kronisk hoste og tetthet i brystet. Personer med KOLS har ofte andre sykdommer som bl.a. angst og hjerte-karsykdom. Diagnosen KOLS stilles på bakgrunn av lungefunksjonsmålinger, og alvorlighetsgrad av luftveisobstruksjon er inndelt i fire nivåer; grad 1 til grad 4. I 2011 ble det foreslått en ny inndeling av KOLS som i tillegg til lungefunksjon tar hensyn til symptombyrde og antall tidligere forverrelser. Personer med KOLS grad 1-2 og færre enn to forverrelser siste år tilhører gruppe A hvis de har lav symptombyrde og gruppe B hvis de har høy symptombyrde. Tilsvarende tilhører personer med KOLS grad 3-4 eller minst to forverrelse siste år gruppe C hvis de har lav symptombyrde og gruppe D hvis de har høy symptombyrde.

Artiklene i avhandlingen er basert på data fra Lungeprosjektet i Helseundersøkelsen i Nord-Trøndelag 1995-97. I en tverrsnittstudie med 10 693 deltakere fant vi at både redusert lungefunksjon og angstsymptomer hadde sammenheng med mer rapportering av tung pust. Innen samme nivå av lungefunksjon var tung pust mer vanlig blant personer med enn blant personer uten angst. Dette kan bety at angst har betydning for opplevelse av tung pust.

I en kohortstudie hvor 10 491 deltakere ble fulgt i opptil 16 år fant vi at redusert lungefunksjon hadde sterk sammenheng med økt totaldødelighet og hjerte-kardødelighet. «Tung pust ved gange» hadde sammenheng med økt totaldødelighet uavhengig av lungefunksjon. «Kronisk hoste», «tung pust i ro» og antall luftveissymptomer hadde sammenheng med økt totaldødelighet kun når lungefunksjon ikke var tatt hensyn til. Luftveissymptomene hadde ikke sammenheng med hjerte-kardødelighet uavhengig av lungefunksjon. Resultatene indikerer at «tung pust ved gange» bør tas på alvor.

Vi fulgte en kohort av 1540 personer med KOLS i opptil 16 år og fant at dødeligheten økte gradvis fra KOLS grad 1 til grad 4, mens det var liten forskjell i dødelighet mellom gruppene A og B og gruppene C og D. KOLS-gradene predikerte død bedre enn ABCD-gruppene. Inklusjon av symptombyrde og antall forverrelser ser derfor ikke ut til å oppveie det at lungefunksjon blir redusert til kun to nivåer i ABCD-gruppeinndelingen av KOLS.

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Trondheim, May 2013

Linda Leivseth

LIST OF PAPERS

This thesis is based on the following papers:

Paper I

Leivseth L, Nilsen TI, Mai XM, Johnsen R, Langhammer A. Lung function and anxiety in association with dyspnoea: The HUNT Study. *Respir Med* 2012;**106**:1148-57

Paper II

Leivseth L, Nilsen TI, Mai XM, Johnsen R, Langhammer A. Lung function and respiratory symptoms in association with mortality: The HUNT Study. *Copd.* Published Online First: 22 July 2013. doi:10.3109/15412555.2013.781578

Paper III

Leivseth L, Brumpton BM, Nilsen TI, Mai XM, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: The HUNT Study, Norway. *Thorax* 2013;**68**:914-921

ACRONYMS AND ABBREVIATIONS

AUC	Area under the receiver operating characteristic curve
BD	Bronchodilator
BMI	Body mass index
CAT	COPD Assessment Test
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DM	Diabetes mellitus
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOLD 1	$FEV_1/FVC < 0.70$ and $ppFEV_1 \geq 80$
GOLD 2	$FEV_1/FVC < 0.70$ and $50 \leq ppFEV_1 < 80$
GOLD 3	$FEV_1/FVC < 0.70$ and $30 \leq ppFEV_1 < 50$
GOLD 4	$FEV_1/FVC < 0.70$ and $ppFEV_1 < 30$
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HUNT	Nord-Trøndelag Health Study
HUNT1	Nord-Trøndelag Health Study 1984-86, Survey 1
HUNT2	Nord-Trøndelag Health Study 1995-97, Survey 2

HUNT3	Nord-Trøndelag Health Study 2006-08, Survey 3
HUNT4	Nord-Trøndelag Health Study 2017-19, Survey 4
ICD	International Classification of Diseases
LLN	Lower limit of normal
mMRC	modified Medical Research Council
NRQ	Norwegian Respiratory Questionnaire
OR	Odds ratio
PH	Proportional hazard
$ppFEV_1$	Per cent predicted FEV_1
ppFVC	Per cent predicted FVC
SBP	Systolic blood pressure
SGRQ	St. George's Respiratory Questionnaire
SMR	Standardised mortality ratio
VC	Vital capacity

SUMMARY

Background

Chronic obstructive pulmonary disease (COPD) is a considerably underdiagnosed disease with high morbidity and mortality. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the diagnosis is based on post-bronchodilator lung function measurements, and the airflow limitation is classified in four spirometric GOLD grades. In 2011, GOLD launched a new combined assessment of COPD which included symptom burden and exacerbation history in addition to airflow limitation. People with GOLD 1-2 and less than two exacerbations last year were placed in group A if they had low symptom burden, and in group B if they had high symptom burden. Correspondingly, people with GOLD 3-4 or at least two exacerbations last year were placed in group C if they had low symptom burden, and in group D if they had high symptom burden. Symptoms of COPD include dyspnoea, chronic cough, and wheeze. People with COPD commonly have comorbidities like anxiety and cardiovascular disease which may have an impact on the prognosis.

Aims

- To examine the independent and combined association of objectively measured lung function and reported anxiety symptoms with the prevalence of dyspnoea in different situations.

- To explore the association of the exposures i) lung function, ii) respiratory symptoms, and iii) lung function and respiratory symptoms combined, with the outcomes all-cause and cardiovascular mortality.
- To examine the association of spirometric GOLD grades and the new ABCD groups with mortality, and to compare their informativeness in relation to mortality.

Methods

We used baseline data from the Nord-Trøndelag Health Study 1995-97 Lung Study. Three studies were conducted; a cross-sectional study of 10 693 people from the general population; a cohort study of 10 491 people from the general population; and a cohort study of 1540 people with COPD. We used regression models to study associations between exposures and outcomes, and possible confounders were adjusted for.

Results

- Impaired lung function and anxiety symptoms were positively associated with reporting dyspnoea. Within lung function levels, reporting dyspnoea was more common among people with than among people without anxiety symptoms.
- Lung function was strongly and inversely associated with all-cause and cardiovascular mortality. Dyspnoea when walking was positively associated with all-cause mortality independent of lung function. Chronic bronchitis, dyspnoea when sitting, and number of respiratory symptoms were positively associated with all-cause mortality only when lung function was not controlled for. Respiratory symptoms were not associated with cardiovascular mortality independent of lung function.

- Mortality increased gradually with higher spirometric GOLD grade, while there was little difference in mortality between groups A and B, and between groups C and D. Spirometric GOLD grades predicted mortality better than ABCD groups.

Conclusions

It was more common to report dyspnoea among people with than among people without anxiety symptoms within lung function levels. This indicates that anxiety may be important for the experience of dyspnoea. Lung function was strongly and inversely associated with all-cause and cardiovascular mortality. Dyspnoea when walking was positively associated with all-cause mortality independent of lung function, indicating that this symptom should be taken seriously. Spirometric GOLD grades predicted mortality better than ABCD groups. This implies that adding symptom burden and exacerbation history does not compensate for reducing lung function to two levels in the ABCD classification of COPD.

1 INTRODUCTION

This thesis is about associations between lung function, respiratory symptoms, and mortality in a general population, with special focus on chronic obstructive pulmonary disease (COPD). More specifically we have studied associations of lung function and anxiety with reporting dyspnoea, associations of lung function and respiratory symptoms with mortality, and associations of different classifications of COPD with mortality. Our studies are based on data from the large population based Nord-Trøndelag Health Study (HUNT).

This section begins with background information on COPD and current knowledge about lung function, respiratory symptoms, and mortality related to COPD from an epidemiological perspective. In addition, the science of epidemiology is briefly described with special focus on the epidemiological terminology that is used throughout this thesis. The introduction is followed by a description of the data sources, variables, and applied epidemiological and statistical concepts and approaches. After presenting the aims and results, methodological considerations and appraisal of the main findings are discussed. Finally, the conclusions are presented.

1.1 Chronic obstructive pulmonary disease

1.1.1 Definition and severity

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) currently define COPD as "*a common preventable and treatable disease,… characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gasses. Exacerbations and comorbidities contribute to the overall severity in individual patients.*"[1 2] According to GOLD,[1 2] post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) <0.70 confirms persistent airflow limitation and thus COPD. The severity of COPD is graded based on per cent predicted FEV_1 ($ppFEV_1$).[1 2] Predicted values are based on lung function in healthy people of the same age, height, sex, and race.[3] Table 1 presents the current classification of severity of airflow limitation in COPD according to GOLD.[1 2] Since the first GOLD strategy document was published in 2001,[1 4] both the definition and the staging or grading of COPD have been modified. However, the staging of COPD was based on post-bronchodilator $ppFEV_1$ already in the original GOLD strategy document.[1 4]

Table 1-1 Classification of severity of airflow limitation in COPD according to GOLD

Severity of airflow limitation	**Post-bronchodilator lung function in people with FEV_1/FVC <0.70**
GOLD 1: Mild	$ppFEV_1 \geq 80$
GOLD 2: Moderate	$50 \leq ppFEV_1 < 80$
GOLD 3: Severe	$30 \leq ppFEV_1 < 50$
GOLD 4: Very severe	$ppFEV_1 < 30$

Abbreviations: COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; $ppFEV_1$ – per cent predicted FEV_1.

In the 2011 revision of the GOLD strategy document, a new ABCD classification of COPD was presented for the first time.[1 2 5] The goal of this ABCD classification was to determine the severity of COPD in order to guide therapy, and it included assessment of the severity of airflow limitation, the impact on a person's health status through symptom burden, and the risk of future events such as exacerbations and death. According to GOLD,[1 2] symptom burden should be measured by the modified Medical Research Council (mMRC) dyspnoea scale[6] or the COPD Assessment Test (CAT),[7] and exacerbation risk by the GOLD grades of airflow limitation or exacerbations history. The ABCD classification is based on a 2x2 table with cells labelled A, B, C, and D (Figure 1-1). Symptom burden is divided into low (A and C) and high (B and D), whereas airflow limitation and/or exacerbation history separates A from C, and B from D. Regarding the latter, patients should be placed in the group that gives the highest exacerbation risk according to airflow limitation (GOLD 1-2) or exacerbation history (≥2 last year).

GOLD grade	**Symptoms** mMRC <2 or CAT <10	mMRC ≥2 or CAT ≥10	**Number of exacerbations last year**
4 3	**C**	**D**	≥2
2 1	**A**	**B**	<2

Abbreviations: CAT – COPD assessment test; COPD – chronic obstructive pulmonary disease; GOLD – Global Initiative for Chronic Obstructive Lung Disease; mMRC – modified Medical Research Council dyspnoea scale.

Figure 1-1 ABCD classification of COPD according to GOLD

Although the GOLD strategy document define COPD according to a fixed ratio of post-bronchodilator $FEV_1/FVC < 0.70$,[1 2] it is still being debated whether the lower limit of normal (LLN) is a more appropriate diagnostic criteria for COPD.[8-11] LLN values of FEV_1/FVC are based on the frequency distribution of a healthy population, and it classifies the bottom fifth percentile as abnormal.[1 8]

1.1.2 Spirometry

The dynamic lung function measures FVC and FEV_1, which are used to define COPD, are obtained from spirometry.[1 2] FVC may be defined as "*the maximal volume of air exhaled with maximally forced effort from a maximal inspiration*".[12] FEV_1 may be defined as "*the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration*".[12] In order to obtain acceptable and valid measurements, the quality of the spirometric equipment needs to be controlled regularly following specific procedures.[12] Likewise, the test procedure needs to be performed in an optimal manner.[12] It is particularly important that the tested person receives clear and understandable instruction, and that the instructor is enthusiastic and encouraging in order to make the tested person fully exhale. When the manoeuvre is completed, the test results need to be quality assured by automated and manual inspection.[12] The biggest challenge when obtaining lung function measures in order to diagnose COPD is to get valid measures of FVC, mainly because the tested person does not fully inhale or exhale. If the obtained FVC is underestimated, the FEV_1/FVC ratio will be overestimated, and the prevalence of COPD will, hence, be underestimated. On the other hand, FEV_1 is a more robust and reproducible measure as most people will be able to exhale for at least one second.

According to GOLD,[1 2] a diagnosis of COPD should be based on post-bronchodilator lung function. However, post-bronchodilator spirometry is time consuming and not performed as frequently as recommended.[13 14] Often, only pre-bronchodilator lung function is available in clinical practice or in epidemiological studies. Pre- and post-bronchodilator lung function has been found to predict mortality to the same degree in a general population,[15] while post-bronchodilator lung function has been found to predict mortality better than pre-bronchodilator lung function in a clinical cohort.[15]

GOLD recommends to perform spirometry in any person over 40 years presenting with dyspnoea, chronic cough with or without phlegm, a history of exposure to cigarette smoke or other noxious particles or gasses, or with a family history of COPD.[1 2]

1.1.3 Symptoms

People with COPD may or may not experience respiratory symptoms like dyspnoea, chronic cough, chronic bronchitis, wheezing, or chest tightness.[1 2] Dyspnoea, which is a subjective experience of breathing discomfort,[16] is often chronic and progressive in COPD.[1 2] However, dyspnoea develops gradually and people with undiagnosed COPD may reckon dyspnoea during various activities as expected consequences of getting older, having smoked for many years, or being overweight, and they may compensate by avoiding activities causing dyspnoea. Chronic cough with or without phlegm is often an early symptom of COPD that gets progressively worse.[1] Chronic bronchitis, defined as coughing with phlegm for three or more months in two consecutive years,[1] is also a hallmark symptom of COPD. However, people with undiagnosed COPD may consider chronic cough as a natural consequence of smoking or environmental exposures. Some people with COPD experience wheezing and

chest tightness that varies within and between days.[1] Because many people with undiagnosed COPD reckon their respiratory symptoms as natural consequences of the aging process or their lifestyle, COPD is often moderate or severe when finally diagnosed.

In addition to respiratory symptoms, people with severe COPD may suffer from other symptoms like fatigue, weight loss, anorexia, and ankle swelling.[1] As a consequence of inactivity, skeletal muscle dysfunction may lead to exercise intolerance and poor health status.[17] Further, health related quality of life has been found to decrease with higher GOLD grade.[18 19]

1.1.4 Exacerbations

GOLD defines an exacerbation of COPD as "*an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication*".[1 2 20-22] Two or more exacerbations per year are regarded as "frequent".[23] Exacerbations may increase the decline in lung function,[24] the deterioration in health status,[25] and the risk of death.[1] There are also considerable socioeconomic costs associated with exacerbations.[26]

1.1.5 Comorbidities

People with COPD commonly have comorbidities that have an impact on the prognosis.[27-30] The most common and important comorbidities in COPD include cardiovascular disease (CVD),[28-34] diabetes mellitus (DM),[28 33] metabolic syndrome,[33] respiratory infections,[33 35] osteoporosis,[30 33] lung cancer,[29 34] anxiety,[36 37] and depression.[36-38] GOLD encourages medical doctors to actively look for comorbidities in people with COPD. In addition, GOLD generally

suggests that comorbidities should be treated as if the patient did not have COPD, and that the presence of comorbidities should not alter COPD treatment.[1 2]

1.1.6 Factors influencing development and progression

Although there is no doubt that cigarette smoke may cause COPD,[39-42] other factors may also influence disease development and progression. As with most diseases, COPD results from a gene-environment interaction. The best documented genetic condition that causes COPD is alfa-1-antitrypsin deficiency.[42-44] However, other genetic factors are believed to be related to susceptibility to develop COPD or lung function decline when interacting with environmental factors.[45-48] In addition to cigarette smoke,[39-42 49-51] exposure to other particles or gasses such as organic and inorganic dusts, [42 49 52 53] chemical agents and fumes,[42 52 53] biomass and coal,[54 55] and air pollution[42 56] may increase the risk of developing COPD.

Although it is unclear whether healthy aging per se leads to COPD or if age reflects the sum of cumulative exposures to harmful factors throughout life,[1] the prevalence of COPD increases with age.[51 57-63] COPD was previously more common in men than in women in developed countries, but the prevalence of COPD among women and men are now approaching each other.[63] This may reflect changes in smoking habits of women and men.[64-66] In addition, several studies suggest that women are more susceptible to cigarette smoke than men.[67-72]

The risk of COPD may be increased in people with reduced maximal attained dynamic lung function.[73] Hence, any factor that reduces lung development and growth during gestation and childhood may potentially increase the risk of COPD. Such factors include smoking during pregnancy and childhood exposure to environmental tobacco smoke.[42 49 74]

In addition to a family history of asthma,[74 75] respiratory diseases such as asthma,[74 76 77] bronchial hyper-responsiveness,[75] chronic bronchitis,[78-80] and severe respiratory infections in childhood[42 74 75 81] have been suggested to increase the risk of developing COPD. Although low socio-economic status is associated with an increased risk of developing COPD,[82-84] it may reflect other risk factors for COPD such as exposure to cigarette smoke, air pollution, infections, and poor nutrition.

1.1.7 Other terms

COPD has gradually been accepted as a common term for chronic obstructive pulmonary diseases.[8] However, conditions compatible with COPD have previously been called a number of different terms including chronic airflow limitation, chronic airflow obstruction, chronic airways obstruction, chronic lower respiratory disease, chronic non-specific lung disease, chronic obstructive airways disease, chronic obstructive lung disease, chronic obstructive respiratory disease, and non-reversible obstructive airways disease. It is commonly agreed that COPD includes chronic bronchiolitis or bronchitis and emphysema,[8 42] and there is growing evidence that fixed airflow obstruction in people with a history of asthma should be identified and treated as asthma and not COPD.[85]

1.1.8 Prevalence and incidence

The prevalence, also known as prevalence proportion, point prevalence, or prevalence rate, is a measure of disease status.[86 87] The prevalence of COPD is the number of people with COPD in a population divided by the total number of people in the same population at a

specific point in time. Although the prevalence is affected by both the occurrence and the duration of the disease, it is a useful measure of the disease burden in a population.[86]

The frequency of disease onset or occurrence of disease, commonly referred to as incidence, is usually assessed by the two measures incidence proportion and incidence rate.[86 87] The incidence proportion or risk of COPD is the number of newly developed cases of COPD over a specific time period divided by the total number of people at risk of developing COPD during the same time period. Incidence proportion ranges from 0 to 1 and can be interpreted as a probability.[86] However, the incidence proportion is practically impossible to measure over a sufficient time period since some people originally under risk of getting COPD will probably die during the follow-up time or they may get lost to follow-up for other reasons.[86] Due to the problems with measuring the incidence proportion, epidemiological studies usually estimate the incidence rate as a measure of disease occurrence. The incidence rate of COPD is the number of newly developed cases of COPD in a population over a specific time period divided by the total time at risk of developing COPD of all people in the same population during the same time period. Incidence rate ranges from 0 to infinity and can be interpreted as the inverse of waiting time.[86]

It is difficult to obtain good and comparable estimates of the prevalence and the incidence of COPD in different populations due to differences in diagnostic criteria, survey methods, and analytical approaches.[59 88-90] Some studies base the estimates on self-reported COPD or self-reported doctor diagnosed COPD. However, this is likely to underestimate the prevalence or incidence as COPD is considerably underdiagnosed.[1 2 13 14 51 84 91-96] Others have based their estimates on respiratory symptoms. However, respiratory symptoms are also common in people without COPD, and not all people with COPD experience respiratory

symptoms.[1 13] During the last decades, most studies have defined COPD based on lung function measurements.[89] However, some define COPD from pre-bronchodilator lung function, some from post-bronchodilator lung function, some from the GOLD fixed ratio, and others from the LLN.[89] In addition, the many different names on COPD may have led to confusion about what has actually been studied. Different distributions of age, sex, race, education, smoking habits, and other characteristics in different populations may impact the estimated prevalence and incidence of COPD greatly.[89] In addition, the time period of which incidence proportion has been estimated varies between studies.

Several studies have aimed to estimate the prevalence or incidence of COPD in different populations despite these challenges.[59 89 97 98] In a systematic review and meta-analysis from 2006, the estimated pooled prevalence of COPD defined by spirometry was 9.2% based on data from 26 studies from different countries.[89] However, which age groups were included in these studies were not specified. In addition, only nine of these 26 studies used post-bronchodilator lung function measurements.[89] Among six European studies the prevalence of COPD defined as FEV_1/FVC <0.70 varied between 10.2% and 26.1% in the general adult population.[98] In general, the prevalence of COPD varied greatly with age, smoking status, sex, and geographic region.[59 89 97 98]

Table 1-2 presents estimates of the prevalence of COPD in the Nordic countries from selected studies published since year 2005. In summary, the prevalence of post-bronchodilator COPD defined as FEV_1/FVC <0.70 varied between 7% and 19% depending on location, age of participants, and year of study. The prevalence of COPD was generally higher among men than among women.

Table 1-2 Estimated prevalence of COPD in the Nordic countries from selected studies published since year 2005

Location (Year of study)	First author (Publication year)	N	Response rate (%)	Age (years)	Spirometric COPD definition	Prevalence of COPD (%) Total	Women	Men
Norway								
Bergen (2006)	Buist[59] (2007)	707	68	40 +	◆ Post-BD FEV_1/FVC <0.70	18.8	15.4	22.6
					◆ Post-BD FEV_1/FVC <0.70 + $ppFEV_1$<80	8.3	5.9	11.0
Hordaland County (1996-97)	Johannessen[62] (2005)	2235	77	26-82	◆ Post-BD FEV_1/FVC <0.70	7.0	3.7	10.3
					◆ Pre-BD FEV_1/FVC <0.70	9.6	5.8	13.5
Sweden								
Uppsala (2006-07)	Danielsson[91] (2012)	548	55	40 +	◆ Post-BD FEV_1/FVC <0.70	16.2	14.3	18.2
					◆ Post-BD FEV_1/VC <0.70 + $ppFEV_1$<80	6.7	6.6	6.8
					◆ Post-BD LLN	10.0	NR	NR
Norrbotten County (1996)	Lindberg[93] (2006)	1237	82	46-77	◆ Post-BD FEV_1/FVC <0.70	14.3	NR	NR
					◆ Post-BD $FEV_1/$(VC or FVC) <0.70 + $ppFEV_1$<80	8.1	NR	NR
Norrbotten County (1994-95)	Lindberg[95] (2005)	645	66	23-72	◆ Pre-BD FEV_1/FVC <0.70	14.1	13.0	15.3
					◆ Pre-BD FEV_1/VC <0.70 + $ppFEV_1$<80	7.6	6.8	8.4
Denmark								
Copenhagen (2001-03)	Fabricius[99] (2011)	5299	50	35 +	◆ Pre-BD FEV_1/FVC <0.70	17.4	15.8	19.4
					◆ Pre-BD FEV_1/FVC <0.70 + $ppFEV_1$<80	11.2	10.2	12.4

North Jutland and Viborg Counties (2004-06)	Hansen[100] (2008)	4757	36	45-85	◆	Post-BD FEV_1/FVC <0.70	9.0	7.0	11.0
Finland									
Helsinki (2001-03)	Kainu[84] (2013)	628	57	25-75	◆	Post-BD FEV_1/FVC <0.70	5.9	5.4	6.5
					◆	Post-BD LLN	6.8	5.7	8.5
All parts of Finland (1978-80)	Vasankari[101] (2010)	6364	87	30-74	◆	Pre-BD LLN	NR	2.2	4.7
					◆	Pre-BD LLN + $ppFEV_1$ <80	NR	1.4	3.9
All parts of Finland (2000-01)	Vasankari[101] (2010)	5495	80	30-74	◆	Pre-BD LLN	NR	3.1	4.3
					◆	Pre-BD LLN + $ppFEV_1$ <80	NR	1.5	3.6
Lapland County (1995-96)	Kotaniemi[102] (2005)	683	71	21-70	◆	Post-BD FEV_1/FVC <0.70	9.4	3.7	15.6
					◆	Post-BD FEV_1/VC <0.70 + $ppFEV_1$<80	5.4	2.5	8.6
Iceland									
Reykjavik (2006)	Buist (2007)[59]	758	81	40 +	◆	Post-BD FEV_1/FVC <0.70	17.8	17.5	18.2
					◆	Post-BD FEV_1/FVC <0.70 + $ppFEV_1$<80	8.9	9.3	8.5

Abbreviations: BD – bronchodilator; COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; LLN – lower limit of normal; N – number of participants; NR – not reported; $ppFEV_1$ – per cent predicted FEV_1; VC – vital capacity.

Using data from the Nord-Trøndelag Health Study 1995-97 (HUNT2) Lung Study, we estimated the prevalence of pre-bronchodilator COPD among people 40 years or older in the general population to be 11% among women and 19% among men (Table 1-3). In the Hordaland County Cohort Study, 27% of people with pre-bronchodilator $FEV_1/FVC < 0.70$ had post-bronchodilator $FEV_1/FVC \geq 0.70$.[62] In the HUNT2 Lung Study, the corresponding number was 19% (data not shown). If we assume that 19%-27% of people with pre-bronchodilator COPD do not have post-bronchodilator COPD, data from the HUNT2 Lung Study gives an estimated prevalence of post-bronchodilator COPD of 8-9% among women and 14-16% among men. From Table 1-3 we also see that the estimated prevalence of pre-bronchodilator COPD GOLD 2 was higher than GOLD 1, and that 1.3% of women and 1.9% of men had GOLD 3 or higher.

The cumulative incidence of pre-bronchodilator COPD defined as $FEV_1/FVC < 0.70$ has been estimated to be 6.1% in people aged 18-74 years between 1987-88 and 1996-97 (9 years) in Norway,[94] and 11.0% in people aged 46-77 years between 1996-2003 (7 years) in Sweden.[103] This indicates that 7‰ of the general population aged 18-74 years in Norway[94] and 16‰ of the general population aged 44-77 years in Sweden[103] may develop COPD each year. However, these estimates do not reflect the true incidence of COPD as many of the people being at risk of developing COPD at baseline would have died or got lost to follow-up for other reasons during the follow-up period.[86] However, estimates of the incidence of COPD are lacking, and these Scandinavian figures give an idea of the incidence of COPD that are far better than a wild guess.

Table 1-3 Estimated prevalence of pre-bronchodilator COPD and restrictive lung function impairment among people 40 years or older

	Women			Men		
Lung function[a]	**N[b]**	**%**	**(95% CI)**	**N[b]**	**%**	**(95% CI)**
Normal	16 641	83.8	(81.8-85.7)	13 417	77.4	(75.0-79.8)
COPD	2196	11.1	(9.4-12.7)	3369	19.4	(17.2-21.7)
GOLD 1	659	3.3	(2.3-4.3)	1136	6.6	(5.1-8.0)
GOLD 2	1289	6.5	(5.2-7.7)	1903	11.0	(9.2-12.7)
GOLD 3	229	1.2	(0.7-1.6)	258	1.5	(1.1-1.9)
GOLD 4	19	0.1	(0.1-0.1)	72	0.4	(0.2-0.7)
Restrictive	1027	5.2	(4.0-6.4)	547	3.2	(2.1-4.2)

Abbreviations: CI – confidence interval; COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; N – weighted number of people; $ppFEV_1$ – per cent predicted FEV_1; ppFVC – per cent predicted FVC.

[a] Normal – FEV_1/FVC ≥0.70 and ppFVC ≥80; COPD – FEV_1/FVC <0.70; GOLD 1 – FEV_1/FVC <0.70 and $ppFEV_1$ ≥80; GOLD 2 – FEV_1/FVC <0.70 and 80> $ppFEV_1$ ≥50; GOLD 3 – FEV_1/FVC <0.70 and 50> $ppFEV_1$ ≥30; GOLD 4 – FEV_1/FVC <0.70 and $ppFEV_1$ <30; Restrictive – FEV_1/FVC ≥0.70 and ppFVC <80.

[b] Data on 1921 people from the random sample and 5617 people from the symptom sample were weighted to represent 37 197 people from the general population.

1.1.9 Mortality

According to the Global Burden of Disease Study,[104] COPD was the third leading cause of death globally in 2010 with only ischemic heart disease and stroke as causes of more deaths. In a recent review of European studies, mortality from COPD was 7.2-36.1 per 100 000 people.[98] In 2007, the age standardised annual mortality from COPD per 100 000 people was 13.6 among women and 17.6 among men in Sweden, and 5.4 among women and 25.3 among men in Finland.[98] However, these estimates must be interpreted with caution since few death certificate diagnoses have been verified by autopsy making misclassification bias likely. Studies have indicated that mortality from COPD has increased within the last 30-40 years, and that this increase has been greater in women compared to men.[97] These mortality trends may be explained by trends in smoking prevalence, and that women are tend to be smaller and more susceptible to cigarette smoke than men.[97]

That the case-fatality risk for COPD is high was supported by data from the HUNT2 Lung Study. Among 1540 people with post-bronchodilator COPD, 837 people died during a median of 15 years (18 150 person-years) of follow-up, giving a case-fatality risk of 54% (Paper III). For comparison, 12 994 (20%) of the 65 237 participants in HUNT2 died during the same follow-up period (data not shown). However, these numbers are not directly comparable since the mean age at attendance was 63.6 years among the 1540 people with post-bronchodilator COPD, and 50.4 years among all participants in HUNT2. The mortality among people with post-bronchodilator COPD was highly dependent on the spirometric GOLD grade. The death rate was 30/1000 person-years for GOLD 1, 97/1000 person-years for GOLD 4, and the overall death rate was 46/1000 person-years (data not shown). Comparable mortality estimates and trends have been found in Sweden.[105]

1.2 Background for the papers

1.2.1 Lung function and anxiety in association with dyspnoea

Few studies from the general population have studied the association between lung function and dyspnoea. A cross-sectional study from Norway found an association between airflow limitation and dyspnoea.[106] Dyspnoea has also been found to discriminate well between people with and without bronchial obstruction.[107] However, the association between lung function and dyspnoea has mainly been studied in people with specific diagnoses like asthma and COPD, and results from such studies are inconsistent.[108 109 110]

Anxiety and dyspnoea, which are common among people with obstructive lung diseases,[1 111 112] have been found to explain more of the variation in subjective health status of people with COPD than physiological variables like FEV_1.[113] Studies from the general population suggest that dyspnoea has a stronger association with health related quality of life than lung function.[114 115] Although dyspnoea is a prominent symptom of asthma and COPD,[1 116] it is also a symptom of anxiety, especially in people with panic disorder or hyperventilation syndrome.[112]

A few studies have used data from the general population when studying the influence of psychological status on respiratory symptom reporting taking lung function into account.[117-119] When studying 600 "healthy" never-smokers between 14 and 55 years of age without any respiratory or other major diseases and with normal lung function, Dales et al.[119] found a strong positive association between anxiety and dyspnoea. This was supported by Janson et al.[118] who also found a clear positive association between anxiety and dyspnoea in a cross-sectional epidemiologic study. In their review from 2005 Chetta et al.[120] concluded

that subjects with more psychological symptoms are more likely to report respiratory symptoms.

Similar associations have also been found among people with asthma and COPD.[108 121] Among patients with asthma in general practice, anxiety has been found to help explain symptoms more than lung function and asthma severity.[108] Also Giardino et al.[121] found positive associations between anxiety and shortness of breath after adjusting for lung function in patients with emphysema.

In summary, when we started Paper I there were few published studies from the general population that accounted for lung function when studying the association between anxiety and dyspnoea. The existing studies were relatively old and small, included primarily young people, and did not have sex specific analyses. Large population-based studies with a wide span in age and lung function were therefore warranted.

1.2.2 Lung function and respiratory symptoms in association with mortality

The association between lung function and mortality has been thoroughly studied,[122-137] and there is no doubt that all-cause and cardiovascular mortality increases with lower lung function. However, none of these previous studies have classified participants according to both $ppFEV_1$ and COPD grades, few have done sex specific analyses, and few have had more than 10 000 participants.

Respiratory symptoms have been found to be associated with all-cause and cardiovascular mortality in some studies where lung function has not been accounted for.[138-141] However, results from studies on the association of respiratory symptoms with all-cause and cardiovascular mortality that do control for lung function are inconclusive.[129-137 142] In a

population-based study from the United States, reporting at least one symptom of cough, phlegm, wheeze, or breathlessness increased the hazard for all-cause mortality compared to not reporting any symptom within pre-bronchodilator COPD stages.[130] However, there was no investigation of which respiratory symptoms were responsible for the association with mortality, and the analyses were not sex specific. In other studies,[133 137] dyspnoea, but not chronic bronchitis or wheeze, has been found to be associated with all-cause mortality independent of lung function.

Breathlessness has been found to be associated with cardiovascular mortality in 40-64 years old men after controlling for FEV_1 and baseline myocardial ischemia.[136 137] A Dutch study with over 40 years of follow-up found dyspnoea to be clearly associated with cardiovascular mortality also after adjusting for lung function.[142] However, CVD at baseline was not accounted for and the analyses were not sex specific.[142]

In summary, when we started Paper II it was not clear which respiratory symptoms were possibly associated with all-cause or cardiovascular mortality independent of lung function. Large population-based studies that could control for lung function were therefore warranted.

1.2.3 GOLD classifications and mortality in COPD

When we started working with Paper III in June 2012, there were only two published papers on the association of the ABCD classification of COPD and mortality.[143 144] In the first study, both pre-bronchodilator spirometric GOLD grades and ABCD groups predicted mortality in a general population in Denmark, but which classification that best predicted mortality was not formally tested.[143] In this study, survival was lower in people with relatively high lung

function, few exacerbations, and dyspnoea (group B) compared with people with lower lung function or more exacerbations without dyspnoea (group C). The authors suggested CVD or cancer as possible explanations.[143] However, most analyses were unadjusted and confounding may explain some of the findings. For example, compared to participants in group C, participants in group B were older, had a higher body mass index (BMI), and the prevalence of CVD was higher. The average follow-up was only 4.3 years, and it is possible that the associations will change with longer follow-up duration. In the second study, pooled data from 11 Spanish COPD cohorts showed no difference between post-bronchodilator spirometric COPD grades and ABCD groups in predicting mortality during almost 16 000 person-years.[144] Except from adjustment for cohort in some analyses, other possible confounders were not adjusted for. Neither the Danish study[143] nor the Spanish study[144] presented sex specific results.

In summary, when we started Paper III there was limited knowledge about the association of the ABCD groups with mortality in people with COPD. It was therefore a need for studies on the association of the ABCD groups with mortality, and for studies comparing how the spirometric GOLD grades and the ABCD groups predicted mortality. In addition, studies conducting sex specific analyses were warranted.

1.3 Epidemiology

Epidemiology may be defined as "*the study of the distribution of health-related states and events in populations*".[87] According to Rothman et al.[87] the objective of epidemiological research is usually to obtain precise and valid estimates of the effects of potential causes on the occurrence of disease or death.

In epidemiology, the independent variable is commonly called the "exposure" and the dependent variable the "outcome". The exposure is not necessarily something one is exposed to per se; it might also be characteristics of an individual such as sex, age, lung function, and blood pressure. Possible confounding variables are also regarded as exposures. In cohort studies, common outcomes are occurrence of disease or death.

In order to study associations between exposures and outcomes, epidemiologists use tools from mathematics and statistics. However, epidemiology is much more than simply application of these tools. As stated above, epidemiologists are often interested in estimating the effect, or causal association, of the exposure on the outcome, while what could actually be studied are associations within a specific dataset. Different frameworks have been developed in order to help making causal interpretations of study results. Examples of such frameworks are the sufficient-component cause model, the potential-outcome (counterfactual) model, and causal diagrams like directed acyclic graphs (DAGs).[87] [145] [146] When aiming to draw causal inferences based on epidemiological data, one has to be cautious in order to avoid making incorrect inferences. The epidemiological and statistical concepts and approaches applied in this thesis are described in the materials and methods section. Methodological issues including precision and validity are considered in the discussion.

2 OBJECTIVES

The overall objective of this thesis was to study associations between lung function, respiratory symptoms, and mortality in a general population, with special focus on COPD.

The more specific aims were:

- To examine the independent and combined association of objectively measured lung function and reported anxiety symptoms with the prevalence of dyspnoea in different situations (Paper I).

- To explore the association of the exposures i) lung function, ii) respiratory symptoms, and iii) lung function and respiratory symptoms combined, with the outcomes all-cause and cardiovascular mortality (Paper II).

- To examine the association of spirometric GOLD grades and the new ABCD groups with mortality, and to compare their informativeness in relation to mortality (Paper III).

3 MATERIALS AND METHODS

3.1 The Nord-Trøndelag Health Study

Norway has 19 counties, of which Nord-Trøndelag is located in the central part of the country and consisted of 24 municipalities before 2012 (Figure 3-1). The population of Nord-Trøndelag was stable at about 127 000 inhabitants with net migration out of the county of 0.3% per year in 1996-2000, and less than 3% were non-Caucasians.[147] Nord-Trøndelag is fairly representative of Norway in most aspects including age distribution, morbidity, and mortality.[147] HUNT[148] is a large population health survey which has been conducted in Nord-Trøndelag three times; HUNT1 in 1984-86,[149] HUNT2 in 1995-97,[147] and HUNT3 in 2006-08.[150] HUNT4 is currently being planned, and data collection is expected to start in 2017.[151] This thesis used HUNT2 as baseline data. Detailed information about all variables in HUNT is available from HUNT Databank.[152]

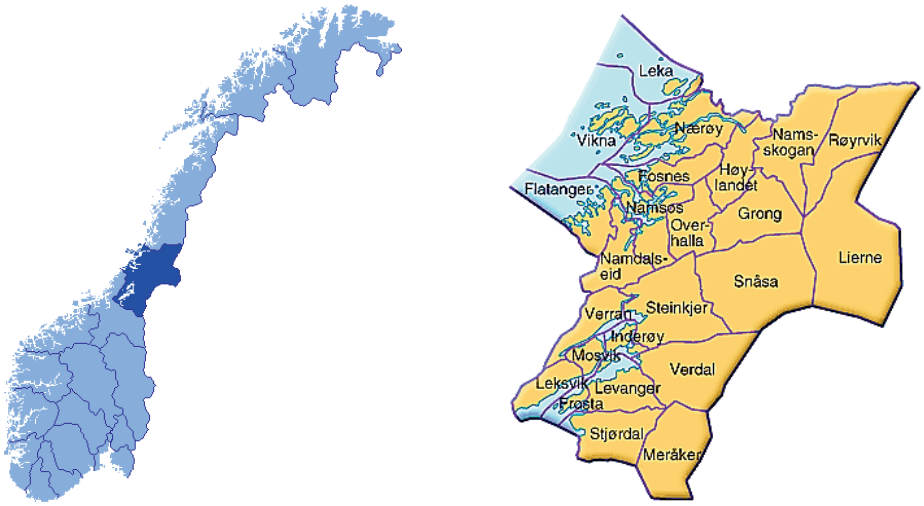

Figure 3-1 Norway and Nord-Trøndelag County with its 24 municipalities

3.1.1 HUNT2

From August 1995 to June 1997, all residents in Nord-Trøndelag County in Norway aged 19 years or older were invited to participate in HUNT2.[147 150] Among 93 898 invited people, 65 237 (69.5%) participated.[148 150] At participation in HUNT2, questionnaire information was collected on a range of lifestyle and health related factors, blood samples were taken, and all participants underwent a clinical examination.[147 150] HUNT2 was a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.[148]

3.1.2 The HUNT2 Lung Study

Among the 65 237 participants in HUNT2, a 5% random sample and a symptom sample were invited to participate in the Lung Study.[153 154] Briefly, the symptom sample included subjects reporting attacks of wheezing or breathlessness during the last 12 months, having ever had asthma, and/or having ever used asthma medication, and who were not included in the random sample. In addition to the information provided by all participants in HUNT2, the Lung Study participants completed a Lung Study questionnaire, a Lung Study interview, and flow volume spirometry.[154] The Lung Study questionnaire and a pre-paid envelope were given to the participants at the screening station, and the participants were asked to fill in the form at home and return it by mail. Flow charts of inclusion and exclusion of study participants in Paper I, Paper II, and Paper III are presented in Figure 3-2, Figure 3-3, and Figure 3-4, respectively. Paper I was a cross-sectional study, while Paper II and Paper III were cohort studies.

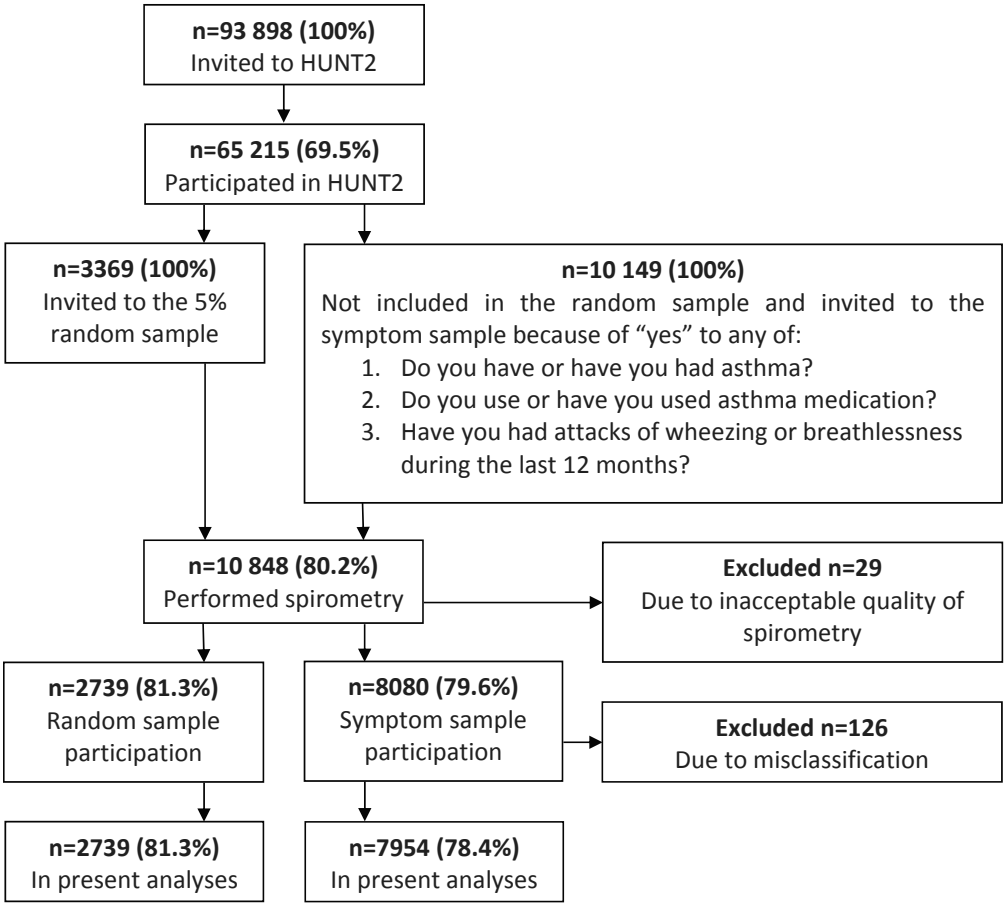

Figure 3-2 Flow chart of inclusion and exclusion in Paper I

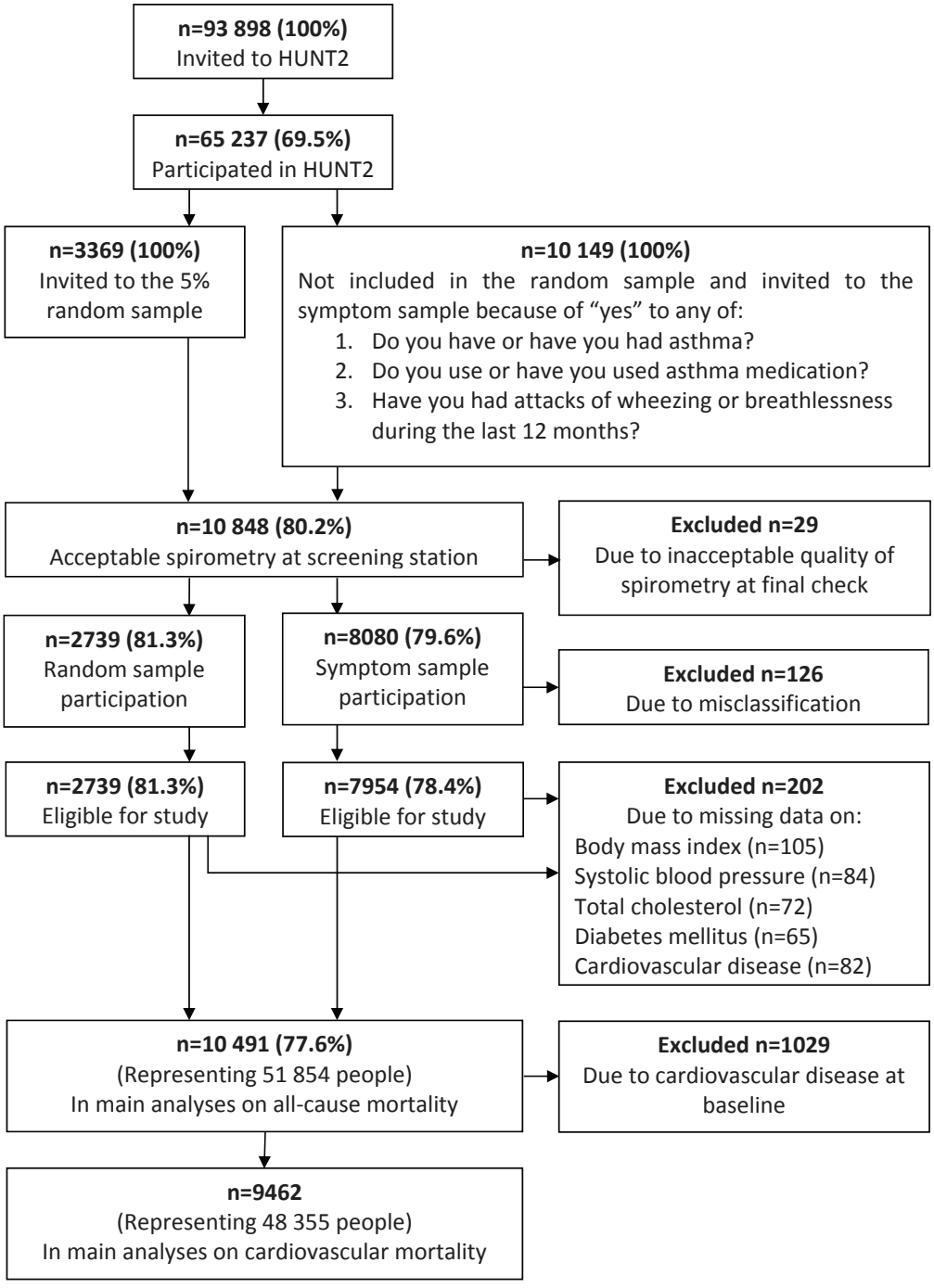

Figure 3-3 Flow chart of inclusion and exclusion in Paper II

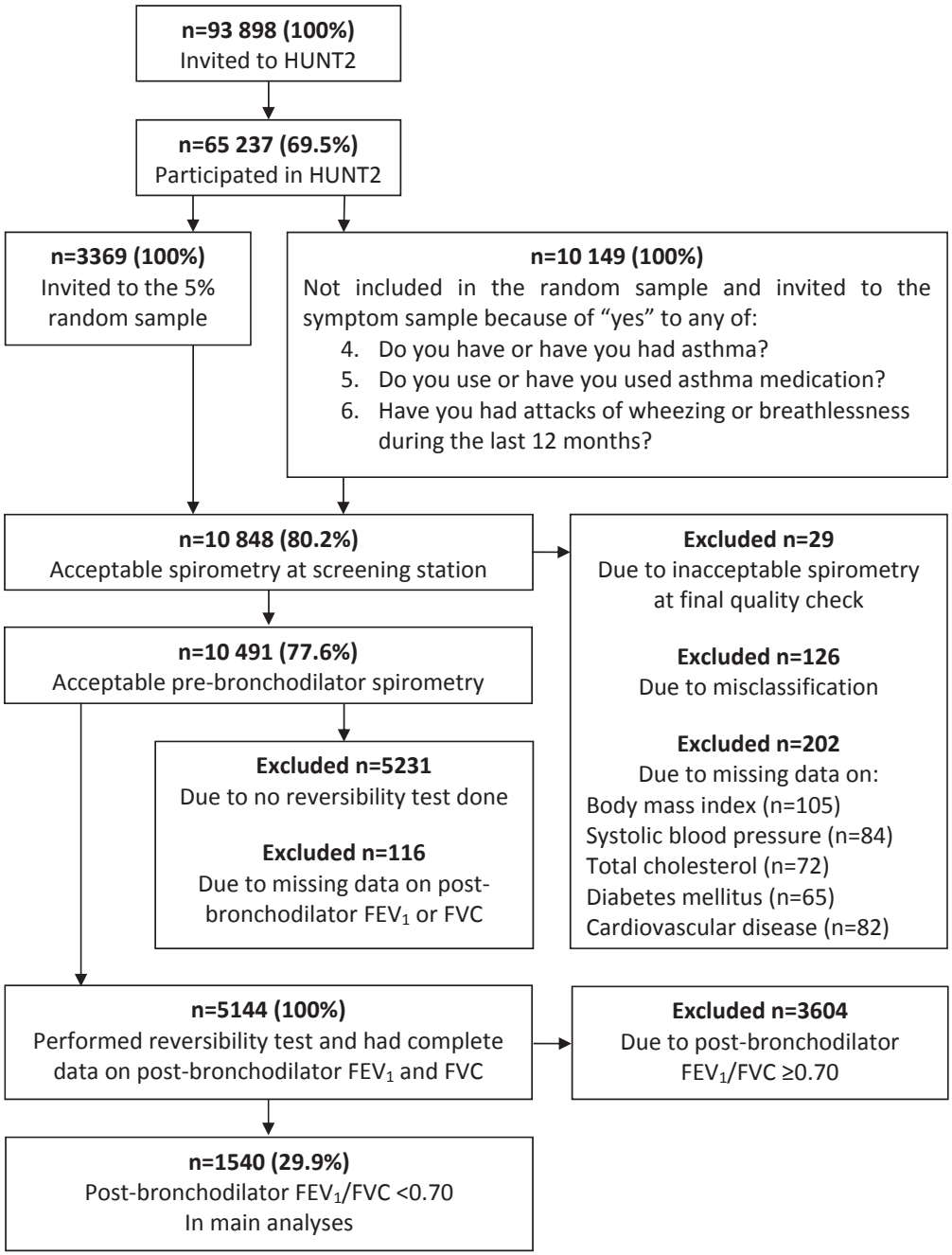

Figure 3-4 Flow chart of inclusion and exclusion in Paper III

3.2 The Norwegian Cause of Death Registry

The Norwegian Cause of Death Registry receives data on all deaths of Norwegian inhabitants.[155] The Norwegian Institute of Public Health owns the registry and controls the data, while Statistics Norway collects and processes the data. Registered causes of death are primarily based on death certificates completed by medical doctors, but the register also collect supplementary information from other sources such as the Norwegian Cancer Registry, the Norwegian Medical Birth Registry, and autopsy reports. The reporting of death by medical doctors and health professionals is mandatory. Causes of death are coded according to the International Classification of Diseases (ICD).[156] Both the underlying and contributing causes of death are registered. Due to the unique 11-digit personal identification number of all Norwegian inhabitants, data from the Norwegian Cause of Death Registry can be linked to other data sources such as HUNT.

3.3 Ethical approval

The Regional Committee for Medical and Health Research Ethics approved the study protocol (reference 4.2008.59), and the Norwegian Data Inspectorate licensed the research register (reference 06/00104-39/CGN). All participants signed informed written consents.

3.4 Study variables

3.4.1 Follow-up and end points

In Paper II and Paper III the participants were followed from the date of attendance in HUNT2 to the date of death (Paper II), to the date of death or emigration (Paper III), or to

the end of follow-up, whichever came first. In Paper II, the end-points were all-cause or cardiovascular (ICD-10: I00-I99) mortality by 31 December 2009. In Paper III, the end-point was all-cause mortality by 24 May 2012.

3.4.2 Anxiety

A Norwegian translation of the Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety.[157] Although the HADS questionnaire was originally developed to measure anxiety and depression in non-psychiatric patients treated in hospitals, it has also been reported to be valid when used in the general population.[158 159] The HADS consists of 14 questions of which seven measure symptoms of anxiety and seven measure symptoms of depression during the past week. Each question is given a score of 0-3, and the total score for each subscale ranges from 0-21. A score of 0-7 indicates normal state, 8-10 borderline state, and 11-21 anxiety state.[158] Psychometric properties of the HADS have been thoroughly tested.[159 160] When one or two answers were missing, the total score was extrapolated by multiplying the sum by 7/6 or 7/5, respectively. In the main analyses anxiety was categorised into three groups; no anxiety (HADS 0-7), borderline (HADS 8-10), and anxiety (HADS 11-21). In the analysis of the combined association of lung function and anxiety, the latter two groups were collapsed into one anxiety symptoms category (HADS 8-21) to increase statistical power. When anxiety was entered as a possible confounder to the association between lung function and dyspnoea, people with missing data on three or more HADS questions were included in a separate category labelled unknown. We studied anxiety as an exposure in Paper I.

3.4.3 Lung function and GOLD grades

Flow volume spirometry was recorded according to the 1994 American Thoracic Society recommendations[161] as described elsewhere.[154] All participants in the HUNT2 Lung Study performed pre-bronchodilator spirometry. A subsample of participants also performed spirometry 30 minutes after inhalation of 1 mg terbutaline, and this subsample was recruited in two ways.[162] In the 19 smallest municipalities all participants were invited, while in the five largest municipalities only participants with pre-bronchodilator FEV_1/FVC <0.75 or $ppFEV_1$ <80 according to the reference values of the European Community for Steel and Coal[163] were invited to perform post-bronchodilator spirometry.[162]

FEV_1 and FVC were obtained, and the prediction equations of Langhammer et al.[154] were used to calculate $ppFEV_1$ and per cent predicted FVC (ppFVC). COPD was defined as FEV_1/FVC <0.70 and airflow limitation was graded according to modified GOLD criteria as GOLD 1 ($ppFEV_1$ ≥80), GOLD 2 (50≤ $ppFEV_1$ <80), GOLD 3 (30≤ $ppFEV_1$ <50), and GOLD 4 ($ppFEV_1$ <30).[1] These grades were called COPD stages in Paper I, COPD grades in Paper II, and GOLD grades in Paper III. In Paper I and Paper II "normal" was defined as FEV_1/FVC ≥0.70 and ppFVC ≥80, and people with possible restrictive lung function impairment (FEV_1/FVC ≥0.70 and ppFVC <80) were excluded from the COPD analyses as they would otherwise have been included in the "normal" category. In Paper III we included only people with COPD defined by post-bronchodilator FEV_1/FVC <0.70.

In Paper I we used pre-bronchodilator lung function as an exposure in two ways; $ppFEV_1$ in categories (≥100, 80-99, 50-79, <50); and COPD stages (normal, stage 1, stage 2, stage 3 or 4). In Paper II we used pre-bronchodilator lung function as an exposure in three ways; $ppFEV_1$ in categories (≥100, 80-99, 50-79, <50); continuous $ppFEV_1$ (for each 10%

decrease); and COPD grades (normal, grade 1, grade 2, grade 3 or 4). In Paper III we used post-bronchodilator lung function as an exposure in two ways; GOLD grades (GOLD 1, GOLD 2, GOLD 3, GOLD 4); and ABCD groups (group A, group B, group C, group D).

3.4.4 Respiratory symptoms

Information on self-reported respiratory symptoms was obtained from the main questionnaire, the Lung Study questionnaire, and the Lung Study interview. The wording of each respiratory symptom question is presented in Table 3-1.

We generated a dyspnoea scale from the four questions about dyspnoea at various activities that were included in the Lung Study questionnaire. These questions were part of the Norwegian Respiratory Questionnaire (NRQ)[164 165] and have previously been used in Norwegian epidemiological studies.[148 165] Each participant was given a score according to the highest level of dyspnoea that the participant ticked as "yes". For comparison, the mMRC dyspnoea scale[6] is presented in Table 3-2. However, it is important to be aware of that studies using different questionnaires are not necessarily comparable since question set-up and exact wording may influence the prevalence of respiratory symptoms.[166]

In Paper I the dyspnoea scale was used as an outcome with cut-offs at "dyspnoea walking" and "dyspnoea sitting still". A third outcome was "woken at night by dyspnoea". In Paper II we used all levels of the dyspnoea scale as an exposure, and we dichotomised the dyspnoea scale at "dyspnoea walking" in analyses where we studied number of respiratory symptoms or dyspnoea combined with lung function as exposures. Additional exposures were "chronic bronchitis" and "wheeze". In Paper III the dyspnoea scale was used as an exposure when we generated ABCD groups. We dichotomised the dyspnoea scale at

Table 3-1 Questions about respiratory symptoms

Respiratory symptom	Question	Answer categories (coding)	Source	Included in Paper
Dyspnoea uphill	"Do you become more short of breath than people your age when walking uphill?"	Yes (1) No (0)	Lung Study questionnaire	
Dyspnoea stairs	"Do you become short of breath when you climb two flights of stairs at normal pace?"	Yes (1) No (0)	Lung Study questionnaire	
Dyspnoea walking	"Do you become short of breath when walking on flat ground at a normal pace?"	Yes (1) No (0)	Lung Study questionnaire	
Dyspnoea sitting still	"Are you short of breath when sitting still?"	Yes (1) No (0)	Lung Study questionnaire	
Dyspnoea scale	(The four dyspnoea questions were combined to a scale where the highest level of dyspnoea the participant had ticked "yes" gave the score)	No dyspnoea (0) Uphill (1) Stairs (2) Walking (3) Rest (4)	Lung Study questionnaire	I II III
Woken at night by dyspnoea	"Have you woken at night because you were short of breath in the last 12 months?"	Yes (1) No (0)	Lung Study interview	I

Wheeze or dyspnoea	"Have you had any kind of attack of wheezing or breathlessness during the last 12 months?"	Yes (1) No (0)	Main questionnaire	III
Dyspnoea at rest	"Have you at any time in the last 12 months been short of breath when resting during the day?"	Yes (1) No (0)	Main questionnaire	III
Chronic bronchitis	"Have you had a cough with phlegm for periods of at least three months during each of the last two years?"	Yes (1) No (0)	Main questionnaire	II
Wheeze	"During the last 12 months, have you had wheezing in your chest at any time?"	Yes (1) No (0)	Lung Study interview	II

Table 3-2 Modified Medical Research Council dyspnoea scale

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise.
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill.
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level.
3	Stops for breath after walking about 100 yards or after a few minutes on the level.
4	Too breathless to leave the house or breathless when dressing or undressing.

"dyspnoea walking" again and used this as a proxy for dyspnoea grade 2 according to the mMRC dyspnoea scale[6] which we ideally should have used according to GOLD.[1] In sensitivity analyses we substituted the dichotomised dyspnoea scale with "wheeze or dyspnoea" and "dyspnoea at rest".

3.4.5 ABCD groups

ABCD groups were generated based on symptom burden and exacerbation risk according to the 2011 revision of the GOLD strategy document.[1 2] Symptom burden was measured by the dyspnoea scale[165] with cut-off on "dyspnoea walking". Exacerbation risk was assessed based on airflow limitation and exacerbation history. Airflow limitation was defined as post-bronchodilator $FEV_1/FVC < 0.70$ and graded as $ppFEV_1 \geq 50$ (GOLD 1-2) or $ppFEV_1 < 50$ (GOLD 3-4). Exacerbation history (<2, ≥2 last year) was generated from two questions; "Have you ever taken cortisone tablets for breathing problems/asthma?" and "How many cortisone courses have you taken in the last year?" We studied the ABCD groups as an exposure in Paper III.

In subsequent sensitivity analyses we regenerated ABCD groups using three alternate measures of symptom burden which had very little or no missing data. For "wheeze or dyspnoea" and "dyspnoea at rest", "no" was regarded as low and "yes" as high symptom burden. The third measure of symptom burden was "How is your health at the moment?" where "good/very good" was regarded as low and "poor/not so good" as high symptom burden.

3.4.6 Possible confounding variables

All analyses were adjusted for **age**. In Paper I and Paper II we adjusted for age at attendance in HUNT2 in 10 year categories (<40, 40-49, …, ≥80 years). In Paper III we adjusted for age as the time scale[167] in the main analyses and continuous age in some additional analyses.

Most analyses were conducted **sex** specific.[168] However, for some analysis in Paper II we combined women and men to increase statistical power, and we adjusted for sex in the model instead.

Education was measured with the question "What is your highest level of education?" which had five answer categories. We categorised education as <10, 10-12, ≥13 years, and unknown in Paper I and Paper II. In Paper III, which included only people with COPD, few participants had high education and we therefore categorised education as <10, ≥10 years, and unknown in this paper.

At the clinical examination height was measured to the nearest centimetre and weight to the nearest half kilogram with participants wearing light clothes and no shoes.[147] **BMI** was computed as weight in kilograms divided by the square of height in metres [kg/m^2]. BMI was categorised according to the World Health Organisation recommendations[169] (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2) in all three papers.

Systolic blood pressure (SBP) was measured three times following standardised procedures,[147] and we used the mean of the second and the third measurement as value for SBP. In Paper II and Paper III we adjusted for SBP in sex specific quartiles [mmHg].

Non-fasting blood was sampled at attendance in HUNT2, and **total cholesterol** was measured following standardised procedures.[147] In Paper II and Paper III we adjusted for total cholesterol in sex specific quartiles [mmol/L].

Participants reporting having ever had angina pectoris (chest pain), myocardial infarction (heart attack), or stroke/brain haemorrhage were classified as having **CVD**. We adjusted for CVD (yes, no) in Paper II and Paper III.

Participants answering "yes" to "Have you had or do you have diabetes?" were classified as having **DM**. We adjusted for DM (yes, no) in Paper II and Paper III.

Depression was measured with the HADS which is described in Section 3.4.2 above. We adjusted for depression (HADS 0-7, HADS 8-10, HADS 11-21, unknown) in Paper I.

Information about **smoking** was obtained from several questions in HUNT2. Pack-years were calculated from numbers of cigarettes smoked daily multiplied by duration of daily smoking and then divided by 20. In Paper I we categorised smoking as never, former and <15 pack-years, former and ≥15 pack-years, current and <15 pack-years, current and ≥15 pack-years, and unknown. In Paper II and Paper III we categorised smoking as never, former, current, and unknown.

Participants were asked to report the average number of hours of low and vigorous physical activity per week in the last year, and answer categories for each question were none, less than 1 hour, 1-2 hours, and 3 hours or more. We combined the two questions and categorised **physical activity** as inactive, light activity <1 hours/week, light activity 1-2 hours/week, light activity ≥3 hours/week, only vigorous activity, and unknown. We adjusted for physical activity in all three papers.

3.5 Statistical analyses

All statistical analyses were conducted using Stata, release 11.1 and 12.1 (StataCorp LP. College Station, Texas). Epidemiological and statistical concepts and approaches applied in this thesis are described in the following subsections.

3.5.1 Directed acyclic graphs

A DAG is a graphical tool that is meant to help researches summarise their qualitative expert knowledge and a priori assumptions about a causal structure of interest.[145] By applying a DAG to the causal structure of interest it may be easier to identify which variables are confounders (common causes) and should therefore be adjusted for in the statistical model, and which variables are colliders (common consequences) or mediators and should therefore not be adjusted for in the statistical model.[87 146 170] Adjusting for a confounder will remove or reduce bias, while adjusting for a collider or a mediator will create bias.[146]

According to Hernán,[145] there are three possible definitions of a confounder. 1) The traditional definition: A confounder must be associated with the exposure, it must be associated with the outcome in the unexposed, and it must not lie on the causal pathway between the exposure and the outcome.[86] 2) The structural definition: A confounder is a common cause of the exposure and the outcome, but not a consequence of either the exposure or the outcome. 3) The causal definition: A confounder is any variable that helps eliminate confounding, or that can be used to block a backdoor path, after conditioning on it.

In the main parts of Paper II and Paper III we presented age-adjusted models and models including variables identified as confounders through DAGs.[87 145] For example, when

studying the association between lung function and mortality, the DAG identified age, smoking, and education as possible confounders (Figure 3-5, Example 1). Although being identified as possible mediators through the DAG in the example, we additionally adjusted for BMI, physical activity, CVD, DM, SBP, and total cholesterol in sensitivity analyses. Nevertheless, the direction of the top left arrow could be questioned for some of the possible mediators, and a change in the direction of the arrow would turn these variables into possible confounders. Hence, it is not absolutely clear whether these variables should be treated as possible mediators or possible confounders. We therefore conducted one model where these variables were treated as possible mediators and one model where these variables were treated as possible confounders.

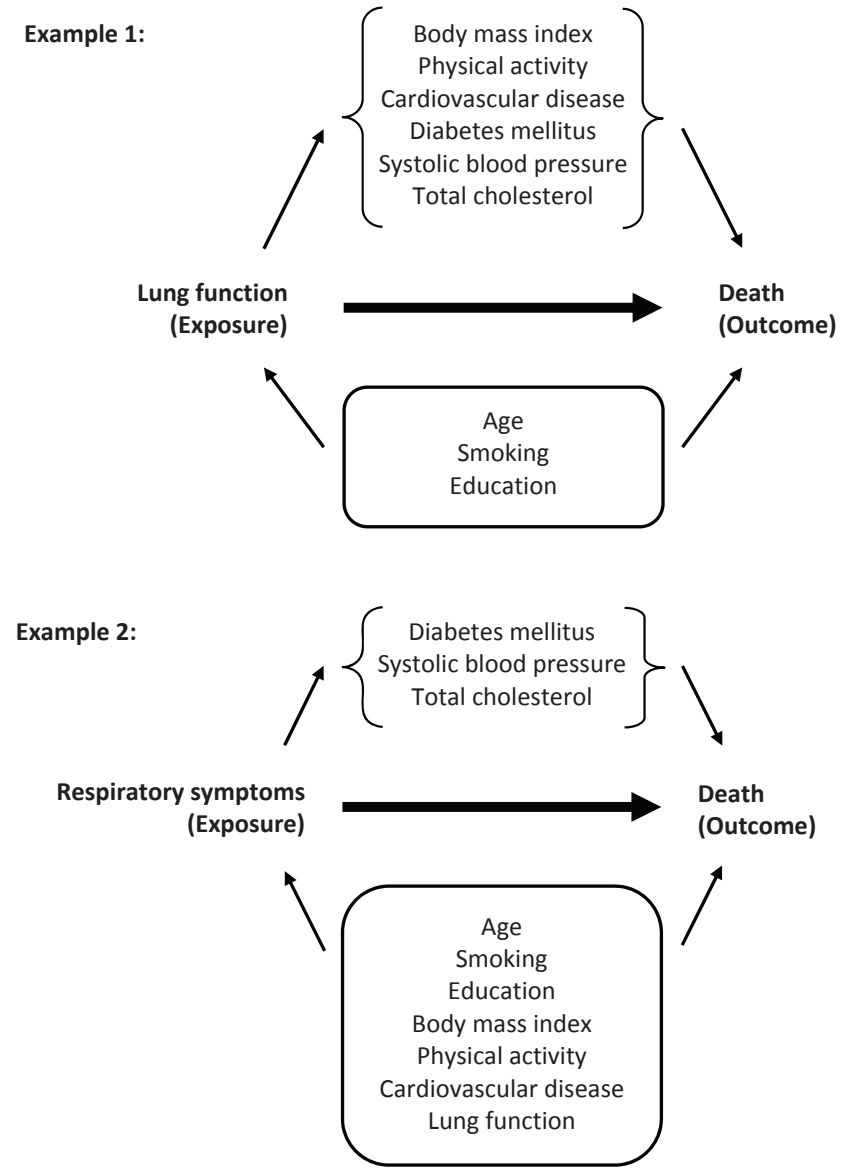

Figure 3-5 Examples of simplified directed acyclic graphs used in Paper II

3.5.2 Inverse probability weighting

Inverse probability weighting is a statistical approach that can be applied to a dataset with the aim of reducing or removing bias,[171] and it is often used in surveys where unequal sampling fractions have been used. Here, sampled people are weighted with the inverse of their probability of being sampled.[171] The HUNT2 Lung Study sampled people in two ways; 1) a 5% random sample (the random sample); 2) everyone reporting attacks of wheezing or breathlessness during the last 12 months, having ever had asthma, and/or having ever used asthma medication in the main questionnaire, and who were not included in the random sample (the symptom sample). This ensured that everyone who fulfilled the inclusion criteria to the symptom sample, whether recruited through the random or the symptom sample, was invited to participate in the HUNT2 Lung Study, and these people were therefore given a weight of 1. People in the random sample who did not fulfil the inclusion criteria for the symptom sample had a 5% chance of being invited to the HUNT2 Lung Study. These were therefore given a weight of 20 since 20 is the inverse of 5%. We could now analyse data as if we had invited all participants in HUNT2 to the HUNT2 Lung Study, and our results could be generalised to the general population of Nord-Trøndelag. However, our inverse probability weights were used on people who actually attended the HUNT2 Lung Study, had valid spirometric measurements, and were not excluded because of missing data. About 20% of people invited to the HUNT2 Lung Study did not fulfil this (Figure 3-2, Figure 3-3, and Figure 3-4). Therefore, instead of representing the 65 237 people who participated in HUNT2, the 10 693 people we had actual measurements on in Paper I represented 53 196 people, and the 10 491 we had actual measurements on in Paper II represented 51 854 people.

In addition to reduce or remove bias caused by unequal sampling fractions, inverse probability weighting can also be used to handle missing data, or to deal with unequal sampling fractions and missing data simultaneously.[171] However, this may result in very complicated weights, and medical statisticians need to be involved to make sure that the weights are being designed correctly. Hence, inverse probability weighting have the potential to deal with several sources of bias. In Paper I and Paper II we used inverse probability weighting to deal with unequal sampling fractions because we wanted to generalise our results to the general population. In Paper III our target population was people with COPD, so inverse probability weighting was not applicable.

3.5.3 Logistic regression

Logistic regression is commonly used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) when the outcome is binary. The OR expresses the odds in favour of success in one exposure category divided by the odds in favour of success in the exposure reference category after adjusting for all other variables in the model.[172] If the exposure is continuous, the OR expresses the relationship between the exposure and the outcome for one unit increase in the exposure variable. An OR of one means that the odds for success in the two compared exposure categories are the same.[173] An OR above one means that the odds for success is increased, while an OR below one means that the odds for success is decreased. The OR can be interpreted as a relative risk (RR) if the outcome is rare.[172-174] However, if the outcome is not rare, the OR will be more extreme than the RR.

We used logistic regression in Paper I to assess the association of lung function and anxiety with dyspnoea, and in Paper III to estimate the area under the receiver operating characteristic curve (AUC) and pseudo R^2 (described in Section 3.5.6).

3.5.4 Survival analysis

Survival analysis may be used when the outcome is the time until an event occurs.[154] Time is commonly referred to as "survival time", and the event is commonly referred to as the "failure". Participants will contribute with person-time from entrance into the study until getting the event of interest or being censored. Reasons for censoring may be that the follow-up time ends, the participant get a competing event, or the participant withdraws from the study or is lost to follow-up.[175] Many analytical approaches in survival analysis assume that the censoring is random, independent, and non-informative.[176] Random censuring means that the failure rate of people who are censured is equal to the failure rate of people who are not censured.[176] Independent censuring means that the censuring is random within sub-groups of interest i.e. that the random censuring is conditional on each level of covariates.[176] If the distributions of time-to-event and time-to-censoring provide no information about each other, the censoring is non-informative.[176] Commonly used approaches in survival analysis are death rates, Kaplan-Meier survival curves, and Cox proportional hazard (PH) regression.

Death rates

Death or mortality rates, which are incidence rates for death,[86] are obtained by dividing the number of deaths by the total time all participants is under risk of dying. We present crude

death rates, and these must be interpreted with caution since they are not adjusted for age or other possible confounders. Death rates are measures of the absolute risk of dying. In Paper II and Paper III we present death rates per 1000 person-years within categories of the exposures.

Kaplan-Meier survival curves

Kaplan-Meier survival curves may be used to graphically present the survival for different categories of an exposure, and they are based on life tables which take censuring into account.[87] However, unadjusted Kaplan-Meier survival curves must be interpreted with caution because apparent associations may be biased by confounding. We used Kaplan-Meier survival curves in Paper III to visualise the association between different classifications of COPD and mortality.

Cox proportional hazard regression

Cox PH regression is commonly used in survival analysis to estimate hazard ratios (HRs) with 95% CIs, and it is based on the Cox model.[175] When information about survival time is available, the Cox model is preferred over the logistic model because the Cox model uses more of the information in the data than the logistic model which ignores survival times and censoring.[175] In addition, the Cox model is considered a robust model, which means that results from the Cox model will closely approximate results from correct parametric models.[175] The HR expresses the estimated hazard of failure in one exposure category divided by the hazard of failure in the reference category after adjusting for all other variables in the model.[172 173] If the exposure is continuous, the HR expresses the relationship

between the exposure and the outcome for one unit increase in the exposure variable. A HR of one means that the hazard for failure in the two compared exposure categories are the same.[173] A HR above one means that the hazard for failure is increased, while a HR below one means that the hazard for failure is decreased.

In Paper II we used Cox PH regression to assess the association of lung function and respiratory symptoms with all-cause and cardiovascular mortality. In Paper III we used Cox PH regression to assess the association of spirometric GOLD grades and ABCD groups with all-cause mortality, and to obtain χ^2-values from likelihood-ratio tests for different predictors of mortality when studying informativeness.

Proportional hazard assumption

The Cox model assumes that the HR comparing any two specifications of an exposure variable is constant over time.[175] This means that the hazard for one individual is proportional to the hazard for any other individual, where the proportionality constant is independent of time.[175] The PH assumption can be assessed in a number of ways using graphical, goodness-of-fit, and time-depending variable approaches.

Graphical approaches include log-log survival curves, observed versus fitted survival curves, and residual plots. A log-log survival curve is a transformation that results from taking the natural logarithm of an estimated survival probability twice which gives a range from minus infinity to infinity. If the vertical distance between the curves is constant, then the curves are parallel. However, how parallel is parallel? It has been suggested to assume that the PH assumption is satisfied unless there is strong evidence that it is not.[175] Another graphical approach for testing the PH assumption is to compare observed versus fitted plots.

Both the log-log approach and the observed versus fitted approach may be carried out by assessing the PH assumption of variables one-at-a-time, or after adjusting for other variables.[175] Continuous variables must be categorised when using any of these approaches. To obtain observed plots, Kaplan-Meier curves are used when assessing variables one-at-a-time, while the stratified Cox model is used when adjusting for other variables. These observed plots are then compared with plots obtained from a fitted Cox PH model. The PH assumption is satisfied if the observed and the fitted plots are "close" to each other. However, how close is close? It has been recommended that the PH assumption is considered not satisfied only when the observed and the fitted plots are strongly discrepant.[175] The third graphical approach for testing the PH assumption is to plot the Schoenfeld residuals versus time.[175] If an increasing or decreasing trend is observed, then the HR is increasing or decreasing over time, respectively, and the PH assumption is violated.

Goodness-of-fit may be assessed by a number of statistical tests. A popular test is based on the Schoenfeld residuals.[175] If the PH assumption holds, than the Schoenfeld residuals are uncorrelated with time. As a general rule, $p>0.10$ implies that the Schoenfeld residuals are uncorrelated with time. However, as with any statistical test the p-value can be driven by sample size.

Time-depending variables included in an extended Cox model may also be used to test the PH assumption.[175] It is possible to test one exposure at-a-time, several exposures simultaneously, and a given exposure adjusted for other variables. However, for this approach we need to choose a function of time to include in the interaction term between the possible time-dependent exposure and time. Unfortunately, different time functions

may give different results. When the PH assumption is violated, the stratified Cox model and the extended Cox model can still be used.[175]

In Paper II and Paper III we assessed departure from the PH assumption by inspecting log-log survival curves, inspecting observed versus fitted plots, calculating Schoenfeld residuals and inspecting plots of the Schoenfeld residuals when the p-value was small, and producing formal tests of interaction with time or log time. Due to a large sample size, small violations of the PH assumption gave significant p-values. We therefore relied mostly on the graphical approaches. In Paper II the PH assumption was not fulfilled when we used age as the time scale. However, when changing to time-of-follow-up as the time scale and instead adjusting for age in 10-year categories, the PH assumption was fulfilled. In Paper III the PH assumption was fulfilled when using age as the time scale.

3.5.5 Standardised mortality ratios

In Paper III we calculated standardised mortality ratios (SMRs) with 95% CIs using the Norwegian population death rates as reference.[177] These death rates were presented separately for women and men, 5-year age bands (20-24, …, 85-89, ≥90), and 5-year calendar periods (1991-1995, …, 2006-2010, 2011). By sorting our data in the same way we calculated the expected number of deaths within the exposure categories in our study cohort. SMRs were obtained when comparing the observed to the expected number of deaths. An advantage of using SMRs over HRs is that SMRs compare the death rates in our data with those in the general population, while HRs compare death rates in one exposure category of our data with death rates of another exposure category in our data. Since all participants in Paper III had COPD, we wanted to compare with the general population and

not only with people in GOLD 1 or group A. A disadvantage of using SMRs over HRs is that the SMRs we used were only standardised to sex, age bands, and calendar period, while HRs can be adjusted for a lot of possible confounders. However, which variables to control for should be thoroughly evaluated.

3.5.6 Informativeness

In Paper III we used informativeness to study how well spirometric GOLD grades and ABCD groups predicted mortality. This method of comparing Cox PH regression models was first described by Peto et al,[178] but has later been used by others.[179-181] The informativeness was computed as the difference in twice the log-likelihood between a Cox PH null model (including age as the time scale, smoking, and education) and an alternative model (including spirometric GOLD grades or ABCD groups in addition to all in the null model). This difference approximately follows a chi-square distribution.[174] The greater the difference, the more informative is that particular predictor. To help compare models, we set the most informative model to 100% and compared the other model with this reference.

Additionally, we analysed the AUC and the pseudo R^2 from logistic regression models including the same variables as presented above. The receiver operating characteristic curve is a plot of sensitivity (true positive rate) by 1-specificity (false positive rate). [172 174] The larger the area under the receiver operating characteristic curve, the better the discrimination, i.e. the better the model predicts who will have the outcome and who will not.[174] An AUC of 0.5 indicates no discrimination, while an AUC of 1.0 indicates perfect discrimination.[174] The pseudo R^2 is an approximation to the R^2 used in linear regression models which tells what proportion of the variance of the outcome that can be explained by the exposures.[172] The

most informative model has the highest value of AUC and pseudo R^2. However, since AUC and pseudo R^2 are obtained from logistic regression models, these measures use less of the information in the data than informativeness based on Cox PH regression which allows for censoring. We therefore presented the results based on the Cox PH model as the main results, and provided additional results from the AUC and pseudo R^2 analyses in order to compare with other studies.

3.5.7 Test for trend

Trend tests are used to explore whether there is a dose-response relationship between different exposure categories and the outcome.[172] In Paper I and Paper II we tested for trend in analyses where the exposure categories had a natural hierarchy. Trend tests across $ppFEV_1$ levels were calculated using the sex specific median value within each $ppFEV_1$ level as an ordinal variable in the regression model (Paper I and Paper II). For testing the trend across anxiety levels (Paper I), COPD stages (Paper I), or COPD grades (Paper II) we treated the categories as an ordinal variable.

3.5.8 P-values and confidence intervals

In hypothesis testing, p-values are used to decide whether to accept or reject the null hypothesis. The null hypothesis in epidemiological studies typically states that "there is no association between exposure and outcome in the population".[86 173] The p-value may be defined as the probability of observing as strong an association or a more extreme association as was observed given that the null hypothesis is true and there is no bias in the study, and it relates to the population of interest.[86 173] In medical research it is common to

reject the null hypothesis if the p-value is less than 5%.[86] However, the 5% significant level is not magic. It is rather an arbitrary chosen probability that means that we are willing to reject the null hypothesis of no association between the exposure and the outcome only if there is less than 5% probability that our results are due to chance alone. In other words, we will incorrectly reject a true null hypothesis 5% of the time. A major weakness with the p-value is that it is driven by both the point estimate and the size of the study sample.[86 87] In a large sample, a small point estimate may be statistically significant, while in a small sample, a large point estimate may not be statistically significant. Hence, p-values should be interpreted with caution, and decisions should also be based on other measures such as the point estimate and the CI.

CIs are closely linked to p-values and hypothesis testing, and also CIs relate to the population of interest.[173] A wide CI indicates an imprecise point estimate, while a narrow CI indicates a precise point estimate. However, the width of the CI depends on the standard error, and the standard error depends on the study sample size and the variability in the data.[87 173] Checking if the CI includes the null value related to the null hypothesis of no association between exposure and outcome, which for relative measures like the OR and HR is 1.00, is equivalent to performing a hypothesis test. Hence, interpretations of results should not be based solely on the confidence limits. Rather, the point estimate together with the CI is important to consider as these measures provide information about both the strength and the precision of the association.[86]

In Paper I and Paper II we used p-values when testing for trend. In all three papers we provided 95% CIs along with the point estimates for ORs (Paper I), death rates and HRs

(Paper II and Paper III), and SMRs (Paper III). In Paper II we provided 95% CIs for categorical baseline characteristics because we did weighted analyses.

4 RESULTS

4.1 Paper I

Lung function and anxiety in association with dyspnoea: The HUNT Study

We examined the independent and combined association of lung function and anxiety symptoms with the prevalence of dyspnoea in different situations in a cross-sectional design. The study included 5627 women and 5066 men who participated in the HUNT2 Lung Study.

In general, people with low levels of $ppFEV_1$ were characterised by older age, less education, more inactivity, and a higher proportion was ever smokers. Mean BMI was lowest among people with $ppFEV_1$ <50, and the prevalence of anxiety and depression symptoms increased with lower $ppFEV_1$ among women.

The adjusted ORs for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea increased with lower $ppFEV_1$ or higher COPD stage (all P_{trend} <0.002). Women with $ppFEV_1$ 50-79 had an OR of 5.24 (95% CI 3.04-9.03) for dyspnoea when walking on flat ground compared to women with $ppFEV_1$ ≥100, whereas the corresponding association among men was 4.00 (95% CI 1.67-9.59).

The adjusted ORs for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea increased with increasing anxiety symptoms (all P_{trend} <0.001). Women with anxiety (HADS 11-21) had an OR of 3.39 (95% CI 1.95-5.88) for dyspnoea when walking on flat ground compared to women without anxiety (HADS 0-7), whereas the corresponding association among men was 3.88 (95% CI 1.77-8.50).

In general, having anxiety symptoms increased the adjusted ORs for reporting dyspnoea within $ppFEV_1$ levels or COPD stages. This trend was most evident when lung

function was measured as $ppFEV_1$. Using people with $ppFEV_1 \geq 100$ without anxiety as reference, the OR for reporting dyspnoea when walking on flat ground was 6.23 (95% CI 3.45-11.28) in women with $ppFEV_1 < 80$ without anxiety and 15.14 (95% CI 7.13-32.12) in women with $ppFEV_1 < 80$ with anxiety. The corresponding ORs among men were 5.75 (95% CI 2.23-14.18) and 15.19 (95% CI 4.74-48.64), respectively. Similar patterns were seen for dyspnoea when sitting still and woken at night by dyspnoea. Further adjustments for depression did not materially change the results.

4.2 Paper II

Lung function and respiratory symptoms in association with mortality: The HUNT Study

We explored the association of the exposures i) lung function, ii) respiratory symptoms, and iii) lung function and respiratory symptoms combined, with the outcomes all-cause and cardiovascular mortality. The study included a cohort of 10 491 adults who participated in the HUNT2 Lung Study and were followed through 2009.

In general, participants with low lung function and participants who reported respiratory symptoms tended to be older, be ever smokers, have less education, be inactive, and have more CVD and DM. BMI was lowest among participants with lowest lung function, and highest among participants reporting respiratory symptoms.

The overall all-cause and cardiovascular death rates per 1000 person-years were 9.70 and 2.96 in women, and 13.74 and 4.13 in men, respectively. Compared to participants with $ppFEV_1 \geq 100$ or normal airflow, women and men with $ppFEV_1 < 80$ or COPD grade 2 or higher

had increased all-cause mortality. For every 10% decrease in $ppFEV_1$ the adjusted HRs for all-cause mortality was 1.17 (95% CI 1.09-1.25) in women and 1.23 (95% CI 1.16-1.30) in men.

Cardiovascular mortality was increased in women with $ppFEV_1$ <50 or COPD grade 3 or 4 and in men with $ppFEV_1$ <80 or COPD grade 2 or higher. However, the increased mortality in women was not demonstrated when $ppFEV_1$ was included in the models as a continuous variable. For every 10% decrease in $ppFEV_1$ the adjusted HRs for cardiovascular mortality were 1.03 (95% CI 0.91-1.16) in women and 1.24 (95% CI 1.10-1.39) in men.

Chronic bronchitis, dyspnoea when walking, dyspnoea when sitting (among women only), and number of respiratory symptoms were positively associated with all-cause mortality in models not adjusted for lung function. However, only dyspnoea when walking remained positively associated with all-cause mortality when adjusted for lung function (HR 1.73 [95% CI 1.04-2.89] in women and HR 1.57 [95% CI 1.04-2.36] in men). Within lung function levels, subjects reporting dyspnoea when walking or sitting had generally higher HRs for all-cause mortality than subjects without these symptoms. Similar trends were not seen for chronic bronchitis or wheeze. None of the respiratory symptoms was associated with cardiovascular mortality when adjusted for lung function.

The presented HRs were adjusted for potential confounders identified through DAGs. Additional adjustments for established risk factors for mortality that could be viewed as either possible confounders or mediators did not materially change the results. The results were fairly robust through several sensitivity analyses.

4.3 Paper III

GOLD classifications and mortality in chronic obstructive pulmonary disease: The HUNT Study, Norway

We examined the association of spirometric GOLD grades and ABCD groups with mortality, and compared their informativeness in relation to mortality. The study included a cohort of 1540 people with post-bronchodilator COPD who participated in the HUNT2 Lung Study and were followed until 24 May 2012.

The distribution of participants was 28% in GOLD 1, 57% in GOLD 2, 13% in GOLD 3, and 2% in GOLD 4, in contrast to 61% in group A, 18% in group B, 12% in group C, and 10% in group D. Kaplan-Meier curves demonstrated large difference in survival between the four spirometric GOLD grades among women and men. Among women, there were small differences in survival between groups A and B, and between groups C and D. In contrast, survival was lower among men in group B compared to A, and in group D compared to C.

During a median of 14.6 years (18 150 person-years) of follow-up, 837 people (54%) died. Mortality increased gradually with higher spirometric GOLD grade. Compared to GOLD 1, the HR was 6.97 (95% CI 3.05-15.91) in women and 4.24 (95% CI 2.57-7.00) in men in GOLD 4. Compared to group A, women in group C (HR 2.47 [95% CI 1.62-3.79]) and D (HR 2.43 [95% CI 1.62-3.66]), and men in group D (HR 1.70 [95% CI 1.25-2.29]), had increased mortality. Similar trends were demonstrated by SMRs. In general, mortality did not differ substantially between groups A and B, and between groups C and D. These main results were adjusted for age, smoking, and education as identified through DAGs. The results did not materially change with further adjustments for known risk factors for mortality, or when

using alternate measures of dyspnoea or health status to regenerate ABCD groups in sensitivity analyses.

Spirometric GOLD grades were more informative than ABCD groups at predicting mortality. These findings were supported by additional analyses of AUC and pseudo R^2, and by sensitivity analyses where alternate measures of dyspnoea or health status were used to regenerate the ABCD groups.

5 DISCUSSION

5.1 Summary of the main findings

We studied associations between lung function, respiratory symptoms, and mortality in participants from the HUNT2 Lung Study. Our main findings were that:

- Impaired lung function and anxiety symptoms were positively associated with reporting dyspnoea (Paper I).
- Within lung function levels, reporting dyspnoea was more common among people with than among people without anxiety symptoms (Paper I).
- Lung function was strongly and inversely associated with all-cause and cardiovascular mortality (Paper II).
- Dyspnoea when walking was positively associated with all-cause mortality independent of lung function (Paper II).
- Chronic bronchitis, dyspnoea when sitting, and number of respiratory symptoms were positively associated with all-cause mortality only when lung function was not controlled for (Paper II).
- Respiratory symptoms were not associated with cardiovascular mortality independent of lung function (Paper II).
- Mortality increased gradually with higher spirometric GOLD grade, while there was little difference in mortality between groups A and B, and between groups C and D (Paper III).
- Spirometric GOLD grades predicted mortality better than ABCD groups (Paper III).

5.2 Methodological considerations

In order to interpret findings from epidemiological studies, methodological issues must be considered. An overall goal of epidemiological studies is to estimate with as much accuracy and as little error as possible, and steps can be taken in the design of studies and in the data analysis to improve accuracy and reduce error.[86] Precision and validity will be discussed in the following subsections.

5.2.1 Precision

Precision may be defined as lack of random error, and random error may be described as unexplained variability in the data.[87] Random error may be due to sampling variation, measurement error, or unexplained variation in study variables or in occurrence measures.[87] Precision or the amount of random error in an estimate is indicated by its CI.[86 87] We used 95% CIs as a measure of precision in all three papers.

Increasing the study size or modifying the design of the study may reduce variance and, hence, improve precision of estimates.[86 87] The precision of estimates may also be affected by the number of outcomes, the ratio of exposed to non-exposed, and categorisation of data.[87] In Paper I and Paper II we analysed data of over 10 000 participants, and the outcomes were relatively common. However, the analyses were performed separately for women and men, the exposure variables were categorised, and several categorical potential confounders were adjusted for. All this reduced the precision of the estimates. In addition, we used inverse probability weighting which Stata automatically adjusted for by increasing the variance in order to avoid artificially low variability in the data. In Paper III we studied only 1540 participants using categorisation of data in the same way as

in the first two papers. However, the outcome was very common and we did not use inverse probability weighting resulting in less random error than if we had performed the analyses in the same way as in the first two papers only with fewer participants. The precision of the individual estimates in our studies depended on which variables were included in each analysis, and this precision is reflected by the width of the corresponding CIs.

5.2.2 Validity

Validity may be defined as lack of systematic error, and it is not influenced by sample size.[87] While internal validity refers to the validity of the inferences of study estimates as they pertain to the actual participants in the study, external validity or generalisation refers to validity of the inferences of the study estimates as they pertain to other people outside the actual study.[87] In causal inference, internal validity is a prerequisite of external validity.[87] Systematic error or reduced validity results mainly from selection bias, information bias, and confounding.[87]

Selection bias

If the associations between exposures and outcomes are different between people participating in a study and people eligible for participation, selection bias is present.[87] Selection bias may result from procedures of subject selection and from factors influencing study participation.[86 87]

In HUNT2, 69.5% of those eligible participated.[150] However, this thesis is based on data from the HUNT2 Lung Study which included a 5% random sample and a symptom sample. In Paper I and Paper II we performed inverse probability weighting to make the

distribution of exposures and outcomes in the weighted sample representative of that in the whole HUNT2 population and thereby reduce selection bias. Since mean values and proportions of key variables did not differ much between the weighted and the random sample we believe the weighting fulfilled its purpose. However, since the inverse probability weights were based only on the sampling and not on the actual participation, there may still have been residual selection bias in our estimates if the associations between exposures and outcomes differed between people who participated and people who were eligible to participate in HUNT2 and in the HUNT2 Lung Study. In Paper I we also repeated all analyses in the random sample only, and results were comparable with the results of the weighted sample although imprecise due to few participants.

In Paper III we included 1540 people with COPD who participated in the HUNT2 Lung Study to examine associations between different classifications of COPD and mortality. We do not think that the associations between exposure and outcome in our study are very different from that of other general populations. However, associations between exposures and outcomes among people with doctor diagnosed COPD are likely to differ from those of people fulfilling the spirometric criteria for COPD who participate in general population studies. Population-based studies have identified that less than half of people fulfilling the spirometric criteria for COPD have been diagnosed by a medical doctor,[51 84 91-96] and distributions of participants in GOLD grades or ABCD groups differs in studies from the general population[143 182] and COPD clinics.[144 183]

Unfortunately, about 25% of the participants in the HUNT2 Lung Study did not return the Lung Study questionnaire and had therefore missing data on the dyspnoea scale. Some additional analyses were performed in order to assess potential selection bias because of

this. In Paper II, there were no differences in baseline characteristics among participants with and without data on the dyspnoea scale, and having or missing data on the dyspnoea scale was not associated with all-cause or cardiovascular mortality. In Paper III, alternate measures of dyspnoea or health status were used to regenerate the ABCD groups in sensitivity analyses, and these results were not materially different from the results of the main analysis. Hence, we did not find indications of serious selection bias due to missing data on the dyspnoea scale in Paper II and Paper III.

Information bias

Information bias arises when data about or from study subjects is wrong.[86 87] For categorical variables such information bias is called misclassification and may be non-differential or differential. Non-differential misclassification is unrelated to other variables, it increases similarities between exposure or outcome groups, and will thus usually underestimate an association. However, non-differential misclassification could also overestimate an association if the misclassified exposure or outcome variable has more than two categories.[86 87] Differential misclassification is misclassification that differs according to the value of other study variables, and it is a serious problem that may result in overestimation or underestimation of an association.[86 87]

When obtaining information about study participants through questionnaires there is always a chance for information bias as participants may underreport or overreport certain factors. If we had defined COPD based on self-reported doctor diagnosed COPD instead of lung function measurements, the prevalence of COPD would have been substantially underestimated. It is also likely that people with respiratory symptoms get a COPD diagnosis

more often than people without respiratory symptoms. In these examples, the misclassification would be differential since the misclassification is related to other study variables. There is also a chance for erroneous reporting of respiratory symptoms, use of prednisolone, anxiety, comorbidities, smoking, and physical activity in our studies. However, the effect of such erroneous reporting depends on whether it is related to other study variables or not.

Although we avoided some information bias by defining COPD based on lung function measurements, these measurements may not be perfect either. Since some participants did not fully exhale, their estimated FVC was too low resulting in a falsely high FEV_1/FVC ratio. Hence, some people who actually had COPD may have been misclassified as not having COPD because of measurement error. This is particularly likely to concern people with mild COPD who have a ppFEV_1 ≥80. Hence, the prevalence of mild COPD may be underestimated in our studies. Measurement error may also contribute to misclassification in variables like BMI, SBP, and total cholesterol, but for these variables the measurement error is likely to be unrelated to other study variables resulting in non-differential misclassification. Other variables like age, sex, and education would probably have negligible measurement error.

There may also be a problem with people remembering information from the past in different ways resulting in recall bias. However, in our studies this is only a problem for baseline variables containing information from the past such as when people started smoking and how much they have smoked since they started. For example, people with doctor diagnosed COPD may report having smoked more or less than people without a COPD diagnosis because they know that smoking causes COPD or because of guilt, respectively, even if the two groups have actually smoked exactly the same amount. Recall bias, which

per definition is differential misclassification, is a large problem in case-control studies where the outcome is known when the exposure information is collected.[86 87]

Since most death certificates are not verified by autopsies, some deaths caused by CVD may have been misclassified as deaths from other causes, and vice versa. Misclassification is not a large problem for all-cause mortality since the Norwegian Cause of Death Registry[155] has complete data of all inhabitants in Norway. In addition, people who died of other causes than the outcome of interest and people who moved out of the country were censored in the statistical analyses. Hence, loss to follow-up, which is considered as a major source of bias in population based cohort studies,[87] have probably not caused bias in Paper II and Paper III.

Confounding

Confounding may be defined as confusion of effect, and this implies that bias arises because the effect of the exposure and the effect of other variables are mixed.[86 87] The bias introduced by confounding can both underestimate and overestimate an effect.[86] The properties of a confounder are described in Section 3.5.1. Also variables that are associated with confounders are sometimes thought of and treated as confounders.[87] Epidemiological studies could be designed and analysed in ways that optimise the prevention or removal of confounding.

We controlled for sex and age in all analyses. Possible confounding by sex was mainly controlled for by conducting sex specific analyses.[86] However, in the analyses of combined exposures in Paper II we merged women and men to increase statistical power, and instead adjusted for sex in the regression models. Sex may also be regarded as a potential effect

measure modifier in our studies. As opposed to confounding which one tries to prevent or remove in epidemiological studies, effect measure modification is a property of the effect under study that should be reported.[87] We did not test for effect measure modification by sex in any of our studies. However, we still presented mainly sex specific analyses because women and men differ in many ways including hormonal and immunological determinants,[168] perception and reporting of symptoms,[168 184] and exposure to cigarette smoke or other noxious particles and gasses.[1] In Paper I and Paper II, we adjusted for age in 10-year categories, while in Paper III we used age as the time scale in the Cox regression models because this gives a very fine adjustment for age.[167]

In Paper I we further adjusted for other variables we believed could be associated with both the exposures and the outcomes. However, it could be discussed whether some of these variables could be consequences of the exposure or the outcome or both, resulting in adjustment for colliders or mediators. Nevertheless, we do not think that such possible over-adjustments have materially biased the results since the same trends were seen both for the age-adjusted and the multi-adjusted analyses. We further controlled for confounding by examining the association of lung function and anxiety as a joint exposure with dyspnoea.[86] However, for these analyses we merged some categories to increase statistical power, and this could have resulted in increased residual confounding.

To decide which potential confounders to adjust for in Paper II and Paper III we used prior knowledge to construct DAGs.[145] In Paper II we presented four models with different adjustments. Model 1 - age; Model 2 – also other possible confounders identified through DAGs; Model 3 – also lung function (for the association between respiratory symptoms and mortality); Model 4 – also variables that could be viewed as either possible confounders or

mediators. Model 4 was included because there has been a tradition to adjust for variables known to be associated with mortality, and because the causal relationship between some of these variables and the exposure may not be absolutely clear. When studying the association between respiratory symptoms and mortality, several associations attenuated materially after adjusting for lung function. Hence, lung function seemed to confound the association between respiratory symptoms and mortality. Additionally, we examined the effect of lung function and respiratory symptoms simultaneously by generating jointed exposures of these variables.[86] Generally, the results of the age-adjusted and multi-adjusted analyses did not differ materially.

In Paper III we presented age-adjusted models, and models adjusted for potential confounders identified through DAGs. Again, the results of the age-adjusted and multi-adjusted analyses did not differ materially. For the same reason as for Paper II we additionally adjusted for other variables that are known to be associated with mortality, but this did not materially change the results.

Although we attempted to reduce possible confounding in the analyses, residual confounding cannot be excluded. Residual confounding may result from suboptimal categorisation of the confounder, measurement error in the confounder, or unknown confounders that were not controlled for.[86]

External validity

According to Rothman,[86] [87] generalising from an epidemiological study is based on understanding of the underlying biology, rather than on studying a sample that is statistically representative of a larger source population. Hence, generalisability refers to a biological

representativeness based on scientific knowledge, insight, and conjecture about nature. This implies that generalisability may be affected by a low recruitment proportion only if the association between the exposure and the outcome is different among people participating and people eligible for participation in a study.[86]

The recruitment proportion was relatively high both in HUNT2 and in the HUNT2 Lung Study. We do not suspect that the associations studied were materially different among people participating and people eligible for participation in these studies, although this has not been very well studied. In addition, our results are generally in line with results of similar studies from other populations. Hence, we believe our results can be generalised to other comparable populations.

5.3 Appraisal of the main findings

5.3.1 Lung function and anxiety in association with dyspnoea

In Paper I we found reduced lung function to be associated with increased reporting of dyspnoea, and this was supported by other studies from the general population.[106 107] However, the association between lung function and dyspnoea was not consistent in studies of people with asthma or COPD.[108-110] These inconsistent findings may be due to the limited ability of FEV_1 to reflect hyperinflation as hyperinflation is one of the main causes of dyspnoea in people with obstructive lung diseases.[109]

In line with other studies from the general population[117-119] and studies among people with asthma and COPD,[108 121] we found more anxiety symptoms to be associated with increased reporting of dyspnoea. However, the causal relationships between anxiety

and dyspnoea are unclear.[16] Bailey suggested that dyspnoea may cause anxiety, and anxiety may cause further dyspnoea, and she referred to this as a dyspnoea-anxiety-dyspnoea cycle.[185] Further, findings from a prospective population based study suggested that psychological symptoms like anxiety may cause dyspnoea.[117] In people with COPD, anxiety may cause dyspnoea by increasing respiratory rate and thereby reducing expiration time leading to worse hyperinflation.[109] Since we adjusted for ppFEV$_1$ and depression,[186] it is unlikely that the observed association between anxiety and dyspnoea were explained by these variables unless there was considerable residual confounding.

Although we found more anxiety symptoms to be associated with increased reporting of dyspnoea in three different situations, the causal relationship between anxiety and dyspnoea may differ depending on the situation in which dyspnoea is experienced. One might suspect that anxiety could cause dyspnoea when sitting still, and that experiencing dyspnoea when walking on flat ground or waking up with dyspnoea could cause anxiety. However, our cross-sectional study cannot confirm these speculations, and this needs to be further studied in other study designs. An alternative explanation of our findings may be that the perception of dyspnoea differs among people with and without anxiety. Thus, anxiety may affect the reporting of dyspnoea. Still, when handling patients with obstructive lung diseases, treatment of both airway obstruction and anxiety, if present, are important in order to reduce the total symptom burden.

5.3.2 Lung function and respiratory symptoms in association with mortality

In accordance with findings from previous epidemiological studies,[122-137] [187] we found increased all-cause and cardiovascular mortality with lower lung function. However, none of

these previous studies have classified participants according to both $ppFEV_1$ and COPD grades, and few have done sex specific analyses. For the main analyses of cardiovascular mortality we excluded participants with CVD at baseline to avoid reverse causation. Thus, our results indicate that impaired lung function may be causally associated with cardiovascular mortality. Possible mechanisms that may explain our findings include systemic inflammation, impaired functional capacity, muscle dysfunction, malnutrition, oxidative stress, and comorbidities such as CVD, depression, lung cancer, and DM.[188]

Dyspnoea, but not chronic bronchitis or wheeze, was associated with all-cause mortality independent of lung function in Paper II. Two older studies supported these findings.[133 137] Interestingly, among the four levels of dyspnoea only dyspnoea when walking was associated with all-cause mortality. However, none of the respiratory symptoms remained associated with all-cause mortality independent of lung function when we excluded participants with CVD at baseline, indicating that CVD could explain some of the association between dyspnoea when walking and mortality. Nevertheless, excluding people also resulted in reduced power to detect an association. Future studies aiming at scrutinising the complex mechanisms involved in the sensation of dyspnoea[16] may be needed to explain our findings.

Somewhat unexpectedly, we found no association between dyspnoea and cardiovascular mortality independent of lung function in sex specific models. This lack of association may be due to low statistical power, misclassification of cardiovascular deaths, residual confounding, or it may reflect the reality. Additional analyses combining women and men increased the statistical power, but only the association between dyspnoea when walking and cardiovascular mortality was statistically significant when participants with CVD

at baseline were included. Others have found breathlessness to be associated with cardiovascular mortality in 40-64 years old men after controlling for FEV_1.[136 137] Although these studies did not exclude men with CVD at baseline, they adjusted for baseline myocardial ischemia. A Dutch study with over 40 years of follow-up found dyspnoea to be clearly associated with cardiovascular mortality also after adjusting for lung function.[142] However, CVD at baseline was not accounted for, the analyses were not sex specific, and cardiovascular death was coded differently than in Paper II.[142]

Our results suggested that pre-bronchodilator lung function is strongly and inversely associated with all-cause and cardiovascular mortality, and that dyspnoea when walking may be positively associated with all-cause mortality independent of lung function. More research is needed in order to explore the relationship between dyspnoea and mortality.

5.3.3 GOLD classifications and mortality in COPD

Since the ABCD classification of COPD was launched by GOLD in 2011, the scientific respiratory community has demanded evidence for the choices of symptom and exacerbation measures with cut-offs,[189 190] and evidence for the management suggestions related to the ABCD groups.[190] In addition, it has been indicated that the ABCD groups are too complex to be used in primary care.[190] When Paper III was accepted in March 2013, there were still only three published papers that had studied the association between the ABCD groups and future exacerbations[143 183] or mortality.[143 144] However, just as this thesis was about to be submitted, a fourth paper on comparison of spirometric GOLD grades and ABCD groups for predicting hospitalisation and mortality was published.[191]

In addition to the associations studied by Paper III and the other four papers, the distribution of participants in ABCD groups was of interest to the scientific respiratory community. An overview of such distribution of participants in these five papers is presented in Table 5-1. Among the four studies including people with GOLD 1-4, group D consisted of 32%-41% of the participants from the clinical studies as opposed to 4%-10% of the participants from the population-based studies. Likewise, group A consisted of 29%-34% of the participants from the clinical studies, as opposed to 61%-77% of the participants from the population-based studies. This implies that people in group A are likely to be undiagnosed because they do not experience respiratory symptoms, and they will therefore not be included in clinical studies. Although the age distribution differed between these studies, it is unlikely that many people below 40 years fulfilled the spirometric criteria for COPD and thereby were placed in an ABCD group. The differences in distribution of participants between the population-based study by Lange et al.[143] and our Paper III may partly be explained by the use of pre-bronchodilator lung function by Lange et al.[143] while we used post-bronchodilator lung function. It is likely that some people with pre-bronchodilator COPD would not fulfil the spirometric criteria for COPD if a bronchodilator is applied,[62 192] resulting in fewer participants with mild COPD in our Paper III.

There has also been interest in the distribution of participants according to how people are included in groups C and D. The subgroups of C and D are defined as follows; C1 or D1 – GOLD 3-4 and <2 exacerbations last year; C2 or D2 – GOLD 1-2 and ≥2 exacerbations last year; and C3 or D3 – GOLD 3-4 and ≥2 exacerbations last year. Table 5-3 shows the distribution of participants in these subgroups in Paper III and in the other three studies that has provided information about subgroup distribution. In all four studies, the majority of

Table 5-1 Distribution of participants in ABCD groups in different studies

First author (year)	N	Population	Age (years)	Symptom burden measure	A		B		C		D	
					%	(n)	%	(n)	%	(n)	%	(n)
Leivseth[182] (2013)	1204	General population; GOLD 1-4	19 +	NRQ	61	(731)	18	(216)	12	(142)	10	(115)
Lange[143] (2012)	6628	General population; GOLD 1-4	20-100	mMRC	77	(5126)	14	(936)	4	(271)	4	(295)
Johannessen[191] (2013)	912	Hospital + general population; GOLD 2-4	40-91	mMRC	21	(193)	29	(267)	6	(57)	43	(395)
Soriano[144] (2013)	3163	COPD clinics; GOLD 1-4	66.4 ± 9.7	mMRC	34	(1064)	16	(515)	18	(561)	32	(1023)
Han[183] (2012)	4484	COPD clinics; GOLD 1-4	45-80	mMRC	34	(1507)	21	(919)	8	(355)	38	(1703)
				SGRQ	29	(1317)	25	(1109)	5	(221)	41	(1837)

Abbreviations: A – Dyspnoea < grade 2, GOLD 1-2, and <2 exacerbation last 12 months; B – Dyspnoea ≥ grade 2, GOLD 1-2, and <2 exacerbation last 12 months; C – Dyspnoea < grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months; D – Dyspnoea ≥ grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months; mMRC – modified Medical Research Council dyspnoea scale; N – total number of participants; n – number of participants in each group; NRQ – Norwegian Respiratory Questionnaire; SGRQ – St. George's Respiratory Questionnaire.

Table 5-2 Distribution of participants in the subgroups of C and D in different studies

First author (year)	Measure of exacerbations	Symptom burden measure	C1 Dysp <2 GOLD 3-4 <2 exa		C2 Dysp <2 GOLD 1-2 ≥2 exa		C3 Dysp <2 GOLD 3-4 ≥2 exa		D1 Dysp ≥2 GOLD 3-4 <2 exa		D2 Dysp ≥2 GOLD 1-2 ≥2 exa		D3 Dysp ≥2 GOLD 3-4 ≥2 exa	
			%[a]	(n)	%[a]	(n)	%[a]	(n)	%[a]	(n)	%[a]	(n)	%[a]	(n)
Leivseth[182] (2013)	Prednisolone	NRQ	54	(76)	36	(51)	11	(15)	55	(63)	26	(30)	19	(22)
Lange[143] (2012)	Prednisolone, antibiotics or hospital	mMRC	75	(203)	23	(62)	2	(6)	79	(234)	11	(33)	9	(28)
Johannessen[191] (2013)	Prednisolone or antibiotics	mMRC	75	(43)	18	(10)	7	(4)	69	(273)	10	(40)	21	(82)
Han[183] (2012)	Prednisolone, antibiotics or hospital	mMRC	73	(259)	19	(68)	8	(28)	64	(1096)	13	(222)	23	(385)
		SGRQ	78	(173)	17	(38)	5	(10)	64	(1182)	14	(252)	22	(403)

Abbreviations: C1 – Dyspnoea < grade 2, GOLD 3-4, and <2 exacerbations last 12 months; C2 – Dyspnoea < grade 2, GOLD 1-2, and ≥2 exacerbations last 12 months; C3 – Dyspnoea < grade 2, GOLD 3-4, and ≥2 exacerbations last 12 months; D1 – Dyspnoea ≥ grade 2, GOLD 3-4, and <2 exacerbations last 12 months; D2 – Dyspnoea ≥ grade 2, GOLD 1-2, and ≥2 exacerbations last 12 months; D3 – Dyspnoea ≥ grade 2, GOLD 3-4, and ≥2 exacerbations last 12 months; mMRC – modified Medical Research Council dyspnoea scale; n – number of participants in each group; NRQ – Norwegian Respiratory Questionnaire; SGRQ – St. George's Respiratory Questionnaire.

[a] Per cent of participants within group C or group D.

people are placed in groups C or D because of low lung function alone. However, the proportion of people in C1 and D1 is lower in Paper III compared with the other three studies. This may be explained by differences between studies in measures of airways obstruction, symptom burden, and exacerbations, in addition to different study populations.

The main aim of Paper III was to examine the association of spirometric GOLD grades and ABCD groups with mortality, and to compare their informativeness in relation to mortality. When Paper III was conducted, this had only been studied in the two previous publications of Lange et al.[143] and Soriano et al.[144] The paper of Johannessen et al.[191] was published after the acceptance of Paper III. In their population-based study, Lange et al.[143] found both pre-bronchodilator spirometric GOLD grades and ABCD groups to be associated with mortality, but they did not study which GOLD classification of COPD that best predicted mortality. In addition, this study had an average follow-up of only 4.3 years, most analyses were unadjusted, and analyses were not sex specific. In contrast, both Soriano et al.[144] and Johannessen et al.[191] did compare which of post-bronchodilator spirometric GOLD grades or ABCD groups that best predicted mortality in their respective predominantly clinical cohorts, and both studies concluded that there were no differences. However, the study of Soriano et al.[144] included 93% men, sex specific analyses were not conducted, and most analyses were unadjusted. Johannessen et al.[191] conducted some sex specific sensitivity analyses of which the results did not differ substantially from the results of the combined analyses. In addition, Johannessen et al.[191] presented both unadjusted and adjusted models.

In Paper III we first demonstrated that the HRs for death and the SMRs increased gradually from GOLD 1 to GOLD 4, while there were small differences between groups A and B, and between groups C and D. We further demonstrated that the spirometric GOLD grades

predicted mortality materially better than the ABCD groups. A likely explanation of these findings may be that $ppFEV_1$ is dichotomised at 50 in the ABCD groups resulting in less discrimination between people with different lung function. Hence, the ability to predict mortality seems to be reduced because of fewer lung function categories despite including information about symptom burden and former exacerbation in the ABCD groups.

While Soriano et al,[127] Han et al.,[164] Lange et al.,[143] and our Paper III included people with GOLD 1-4, Johannessen et al.[191] included people with GOLD 2-4. Hence, the different conclusions of Johannessen et al.[191] and Paper III may be explained by the different inclusion criteria. In addition, using GOLD 2 as opposed GOLD 1 as the reference category would give different results. In order to explore the effect of having different inclusion criteria we repeated the main analyses of Paper III excluding people with GOLD 1. In these analyses, mortality still increased with higher spirometric GOLD grade, but differences within spirometric GOLD grades and differences between spirometric GOLD grades and ABCD groups were smaller than in the original analyses (Table 5-3). When excluding participants with GOLD 1, we were no longer able to compare models to assess which GOLD classification that best predicted mortality using a likelihood-ratio-test. In order to have the same degrees of freedom, the two models to be compared must include the same number of variables and categories.[174-176] Therefore, a model with only three spirometric GOLD grades cannot be compared with a model with four ABCD groups.

The different conclusions of Johannessen et al.[191] and our Paper III may also be explained by the application of different analytical approaches, and this should be considered when comparing study results. In Paper III, we assessed informativeness from likelihood-ratio-tests based on adjusted Cox PH models in order to utilise the valuable

information in the data about time-to-event and to adjust for important confounding variables. However, we also reported AUC and pseudo R^2 from adjusted logistic models in order to compare with other studies. Unfortunately, logistic models ignore valuable information about time-to-event. To explore the effect of using different analytical approaches we reanalysed our data using the Stata commands *lroc* and *roccomp*.[193] Using this approach, we too found no difference in predictive ability between spirometric GOLD grades and ABCD groups in unadjusted models including people with GOLD 2-4 (Table 5-4). However, spirometric GOLD grades still predicted mortality better than ABCD groups among women and men in adjusted models including people with GOLD 1-4.

Soriano et al.[144] and Johannessen et al.[191] also used Harrell's C from adjusted Cox PH models to compare the predictive ability of the spirometric GOLD grades and the ABCD groups. The Harrell's C estimates the probability of concordance between predicted and observed responses where a value of 0.5 indicates no predictive discrimination and a value of 1.0 indicates perfect separation of people with different outcomes.[194] In order to compare our data with these two studies, we estimated Harrell's C in unadjusted and adjusted Cox PH models among people with GOLD 1-4 and among people with GOLD 2-4. In general, Harrell's C was larger for spirometric GOLD grades than for ABCD groups among people with GOLD 1-4, but not among people with GOLD 2-4 (Table 5-5).

Table 5-3 Death rates, adjusted HRs, and SMRs with 95% CIs for the associations of spirometric GOLD grades and ABCD groups with all-cause mortality among participants with GOLD 2-4 in the HUNT2 Lung Study

COPD classification	Person-years	Observed deaths	Death rate[c]	(95% CI)	Age-adjusted HR[d]	Multi-adjusted HR[e]	(95% CI)[e]	Expected deaths	SMR[f]	(95% CI)[f]
Women										
GOLD grades[a] (n=411)	**5027**	**214**	**42.57**	**(37.23 to 48.67)**						
GOLD 2	4341	155	35.70	(30.50 to 41.79)	1.00	1.00	(Reference)	91	1.70	(1.46 to 1.99)
GOLD 3	583	52	89.12	(67.91 to 116.96)	2.76	2.71	(1.96 to 3.75)	11	4.72	(3.62 to 6.08)
GOLD 4	102	7	68.55	(32.68 to 143.78)	2.85	3.00	(1.36 to 6.63)	1	5.15	(2.45 to 9.92)
ABCD groups[b] (n=328)	**4022**	**169**	**42.02**	**(36.14 to 48.86)**						
Group A	2213	76	34.35	(27.43 to 43.00)	1.00	1.00	(Reference)	48	1.57	(1.26 to 1.97)
Group B	964	37	38.37	(27.80 to 52.96)	1.29	1.36	(0.91 to 2.04)	18	2.10	(1.57 to 2.82)
Group C	370	26	70.25	(47.83 to 103.18)	2.15	2.70	(1.70 to 4.29)	8	3.27	(2.08 to 5.02)
Group D	475	30	63.16	(44.16 to 90.34)	1.95	2.28	(1.46 to 3.56)	10	2.97	(1.91 to 4.51)
Men										
GOLD grades[a] (n=705)	**7498**	**456**	**60.82**	**(55.48 to 66.66)**						
GOLD 2	6142	327	53.24	(47.77 to 59.34)	1.00	1.00	(Reference)	246	1.33	(1.20 to 1.47)
GOLD 3	1189	110	92.51	(76.74 to 111.51)	1.36	1.43	(1.15 to 1.79)	62	1.77	(1.47 to 2.12)
GOLD 4	167	19	113.58	(72.45 to 178.07)	2.73	2.83	(1.76 to 4.55)	5	3.47	(2.70 to 4.39)
ABCD groups[b] (n=540)	**5796**	**351**	**60.56**	**(54.55 to 67.24)**						
Group A	3362	174	51.76	(44.61 to 60.05)	1.00	1.00	(Reference)	124	1.40	(1.23 to 1.61)
Group B	946	57	60.25	(46.47 to 78.11)	0.97	0.89	(0.65 to 1.21)	42	1.36	(1.04 to 1.76)

Group C	942	67	71.11	(55.97 to 90.35)	1.01	1.04	(0.78 to 1.39)	48	1.40 (1.09 to 1.78)
Group D	546	53	97.15	(74.22 to 127.16)	1.44	1.50	(1.09 to 2.05)	26	2.01 (1.52 to 2.63)

Abbreviations: CI – confidence interval; COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; HR – hazard ratio; $ppFEV_1$ – per cent predicted FEV_1; SMR – standardised mortality ratio.

[a] COPD defined as FEV_1/FVC <0.70 and graded as follows; GOLD 2 = $ppFEV_1$ <80; GOLD 3 = 30≤ $ppFEV_1$ <50; GOLD 4 = $ppFEV_1$ <30.

[b] ABCD groups defined as follows; A = Dyspnoea < grade 2, GOLD 2, and <2 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 2, and <2 exacerbation last 12 months; C = Dyspnoea < grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months.

[c] Per 1000 person-years.

[d] Adjusted for age (as the time scale).

[e] Adjusted for age (as the time scale), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown).

[f] Standardised according to sex, 5 year age bands, and 5 year calendar periods.

Table 5-4 Comparison of AUC from logistic regression models

	GOLD 1-4				GOLD 2-4			
	Women (n=468)[a]		Men (n=736)[a]		Women (n=328)[a]		Men (n=540)[a]	
COPD classification	**AUC**	***P***[b]	**AUC**	***P***[b]	**AUC**	***P***[b]	**AUC**	***P***[b]
Unadjusted models								
GOLD grades[c]	0.620		0.629		0.597		0.583	
ABCD groups[d]	0.580	0.098	0.585	0.013	0.598	0.951	0.582	0.978
Adjusted models[e]								
GOLD grades[c]	0.873		0.889		0.866		0.895	
ABCD groups[d]	0.847	0.006	0.882	0.018	0.854	0.219	0.890	0.040

Abbreviations: AUC - area under the receiver operating characteristic curve; COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; $ppFEV_1$ – per cent predicted FEV_1.

[a] People with missing data on dyspnoea were excluded so that the results from the spirometric GOLD and the ABCD groups could be compared.

[b] *P*-value for testing the null hypothesis that the AUC for spirometric GOLD grades and ABCD groups are the same.

[c] COPD defined as $FEV_1/FVC < 0.70$ and graded as follows; GOLD 1 = $ppFEV_1 \geq 80$; GOLD 2 = $50 \leq ppFEV_1 < 80$; GOLD 3 = $30 \leq ppFEV_1 < 50$; GOLD 4 = $ppFEV_1 < 30$.

[d] ABCD groups defined as follows; A = Dyspnoea < grade 2, GOLD 1-2, and <2 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 1-2, and <2 exacerbation last 12 months; C = Dyspnoea < grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months.

[e] Adjusted for age (continuous), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown).

Table 5-5 Comparison of Harrell's C from Cox proportional hazard models

	GOLD 1-4		GOLD 2-4	
	Women (n=468)[a]	Men (n=736)[a]	Women (n=328)[a]	Men (n=540)[a]
COPD classification	**Harrell's C**	**Harrell's C**	**Harrell's C**	**Harrell's C**
Unadjusted models				
GOLD grades[b]	0.593	0.599	0.578	0.564
ABCD groups[c]	0.567	0.566	0.579	0.564
Adjusted models[d]				
GOLD grades[b]	0.778	0.759	0.757	0.746
ABCD groups[c]	0.759	0.756	0.748	0.747

Abbreviations: COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; $ppFEV_1$ – per cent predicted FEV_1.

[a] People with missing data on dyspnoea were excluded so that the results from the spirometric GOLD and the ABCD groups could be compared.

[b] COPD defined as FEV_1/FVC <0.70 and graded as follows; GOLD 1 = $ppFEV_1$ ≥80; GOLD 2 = 50≤ $ppFEV_1$ <80; GOLD 3 = 30≤ $ppFEV_1$ <50; GOLD 4 = $ppFEV_1$ <30.

[c] ABCD groups defined as follows; A = Dyspnoea < grade 2, GOLD 1-2, and <2 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 1-2, and <2 exacerbation last 12 months; C = Dyspnoea < grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3-4 or ≥2 exacerbations last 12 months.

[d] Adjusted for age (<40, 40-49, …, ≥80 years), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown). Time-of-follow-up as the time scale.

We do not think that spirometric GOLD grades and ABCD groups actually predict mortality differently in Hordaland County compared to Nord-Trøndelag County. This is also indicated by the Kaplan Meier curves of Johannessen et al.[191] which show similar trends as the Kaplan Meier curves of Paper III. However, unadjusted Kaplan Meier curves must be interpreted with caution since possible confounders are unevenly distributed between groups. It would have been interesting to apply the method of Peto et al.[178] for assessing informativeness to the data of Johannessen et al.[191] to see if this changes the conclusion of the study. However, Paper III and the study of Johannessen et al.[191] would still not be completely comparable due to differences in inclusion criteria and length of follow-up. As demonstrated by the additional analyses presented in Table 5-3, Table 5-4, and Table 5-5, the different conclusions of the study of Johannessen et al.[191] and our Paper III seem to be explained by differences in study populations and analytical approaches. This clearly demonstrates the importance of methodological issues in conducting and interpreting study results.

The five published papers on ABCD groups have demonstrated considerable confusion in the terminology used to describe the spirometric GOLD grades and the ABCD groups. A few of these terms are “old GOLD grading”, “GOLD 2007”, “GOLD 1-4”, “new GOLD grading”, “new GOLD 2011”, and “GOLD A-D”. In order to avoid confusion, the scientific respiratory community needs to agree on one specific term for each of the two GOLD classifications of COPD. We do not think that variations of “GOLD 2007” or “old GOLD”, and “GOLD 2011” or “new GOLD”, are appropriate terms because COPD was actually classified in two different ways in the 2011 revision of the GOLD strategy document.[1 2] First, the severity of airflow limitation was graded based on spirometric lung function values, and these grades

were called GOLD 1, GOLD 2, GOLD 3, and GOLD 4. Second, the ABCD classification included the spirometric GOLD grades, symptom burden, and former exacerbations, and patients were classified in group A, group B, group C, and group D. We suggest the terms "spirometric GOLD grades" and "ABCD groups" as we have used them throughout this thesis.

There is obviously a need for more research on how the ABCD groups are associated with or predict future exacerbations and mortality, and how the ABCD groups could best be used to guide treatment. In addition, which measures to include and how to categorise them when generating ABCD groups need further attention. The members of the International Primary Care Respiratory Group Research Network and Board may well be correct when stating that the ABCD groups are not fit for purpose and are too complex to be used in primary care.[190] However, this needs to be properly studied. In Paper III we demonstrated that the spirometric GOLD grades predicted mortality better than the ABCD groups in people with post-bronchodilator COPD from the HUNT2 Lung Study. Other studies from other study populations using other analytical approaches concluded differently.[144 191] Future research needs to have clear and specific aims, be well designed, and be properly conducted, analysed, and interpreted.

6 CONCLUSIONS

In a cross-sectional study design, we found impaired lung function and anxiety symptoms to be positively associated with reporting dyspnoea. In addition, reporting dyspnoea was more common among people with than among people without anxiety symptoms within lung function levels. Thus, in addition to airway obstruction, anxiety may be important for the experience of dyspnoea.

In a cohort study design, we found lung function to be strongly and inversely associated with all-cause and cardiovascular mortality, and dyspnoea when walking to be positively associated with all-cause mortality independent of lung function. However, chronic bronchitis, dyspnoea when sitting, and number of respiratory symptoms were positively associated with all-cause mortality only when lung function was not controlled for, and respiratory symptoms were not associated with cardiovascular mortality independent of lung function. Since dyspnoea when walking may be independently associated with mortality, this symptom should be taken seriously.

Following a cohort of people with COPD, we found mortality to increase gradually with higher spirometric GOLD grade, while there were little differences in mortality between groups A and B, and between groups C and D. Spirometric GOLD grades predicted mortality better than ABCD groups. This implies that adding symptom burden and exacerbation history does not compensate for reducing lung function to two levels in the ABCD classification of COPD.

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PAPERS I-III

Paper I

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Lung function and anxiety in association with dyspnoea: The HUNT study

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Summary
Background: Few studies from the general population have investigated the role of anxiety in reporting dyspnoea. We examined the independent and combined association of lung function and anxiety symptoms with the prevalence of dyspnoea in different situations.
Methods: The study included 5627 women and 5066 men who participated in the Lung study of the Nord-Trøndelag Health Study second survey in 1995–97. In a cross-sectional design we used logistic regression to calculate adjusted odds ratios (ORs) for reporting dyspnoea associated with levels of percent predicted FEV_1 ($ppFEV_1$) and anxiety (Hospital Anxiety and Depression Scale).
Results: Overall, there was a linear inverse association between $ppFEV_1$ and dyspnoea (all $P_{trend} < 0.001$), and a positive association between anxiety symptoms and dyspnoea (all $P_{trend} < 0.001$). In combined analysis, using people with $ppFEV_1 \geq 100$ without anxiety as reference, the OR (95% confidence interval) for reporting dyspnoea when walking on flat ground was 6.23 (3.45–11.28) in women with $ppFEV_1 < 80$ without anxiety and 15.14 (7.13–32.12) in women with $ppFEV_1 < 80$ with anxiety. The corresponding ORs among men were 5.75 (2.23–14.18) and 15.19 (4.74–48.64), respectively. Similar patterns were seen for dyspnoea when sitting still and woken at night by dyspnoea.
Conclusion: Impaired lung function and anxiety symptoms were independently associated with reporting dyspnoea. Within lung function levels, reporting dyspnoea was more common among

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people with anxiety symptoms than among people without. This suggests that, in addition to its relation to reduced lung function, the subjective experience of breathing discomfort may also influence or be influenced by anxiety.

Introduction

The prevalence and burden of obstructive lung diseases are increasing.[1,2] Lung function measurements, in particular forced expiratory volume in one second (FEV_1), are important in the diagnosis of asthma and chronic obstructive pulmonary disease (COPD) and in the physiological staging of COPD.[1,2] However, dyspnoea and anxiety, which are common symptoms among people with obstructive lung diseases,[2–4] have been found to explain more of the variation in subjective health status of people with COPD than physiological variables like FEV_1.[5] Studies from the general population suggest that dyspnoea has a stronger association with health-related quality of life than lung function,[6,7] whereas FEV_1 has been reported to correlate weakly with dyspnoea in people with COPD.[8]

Dyspnoea is a subjective experience of breathing discomfort[9] and a prominent symptom of asthma and COPD.[1,2] However, dyspnoea is also a symptom of anxiety, especially in people with panic disorder or hyperventilation syndrome.[3] Some studies have found associations between anxiety and dyspnoea independent of FEV_1,[10–12] also in people with normal lung function.[13] This indicates that anxiety may explain some of the variation in reported dyspnoea that is not explained by FEV_1.

Previous studies linking lung function, anxiety, and dyspnoea are mainly limited to people with specific diagnoses like asthma and COPD.[14,15] However, a few studies from the general population have found associations between psychological and respiratory symptoms.[11,13,15,16]

The aim of this large epidemiologic study from a general population was to examine the independent and combined association of objectively measured lung function and reported anxiety symptoms with the prevalence of dyspnoea in different situations.

Methods

Study population

All residents of Nord-Trøndelag County in Norway aged 20 years or more were invited to the second survey of the large population-based Nord-Trøndelag Health Study (HUNT 2) between 1995 and 1997. HUNT 2 has been described in detail elsewhere.[17] Among the 65,215 participants who attended the primary screening (69.5% of those invited), about 20% were invited to the Lung study due to limited capacity for spirometric measurements at the screening station. The Lung study consisted of a 5% random sample and a symptom sample.[18,19] The symptom sample included subjects reporting attacks of wheezing or breathlessness during the last 12 months, having ever had asthma, and/or having ever used asthma medication, and who were not included in the random sample. A flow chart of inclusion and exclusion in the Lung study is presented in Fig. 1. Among the 13,518 individuals invited to perform spirometry, 10,848 (80.2%) had acceptable spirometry at the screening station. However, further quality assurance revealed 29 unacceptable spirometric measurements, and these were excluded from the analyses. In addition, 126 subjects were excluded due to misclassification. The analyses included the remaining 10,693 subjects, and these were weighted to represent 53,196 subjects from the general population of Nord-Trøndelag County.

Study variables

All participants in HUNT 2 filled in a general questionnaire on life style factors, complaints, and diseases.[19] Demographic data were recorded. Participants in the Lung study completed an additional lung specific questionnaire and an interview,[19] and performed flow volume spirometry.

Dyspnoea

We used measures of dyspnoea during three different situations; a) dyspnoea when walking on flat ground, b) dyspnoea when sitting still, and c) woken at night by dyspnoea. The lung-specific questionnaire included four questions about dyspnoea at various activities with "yes" or "no" as possible answers: Q1 "Do you become more short of breath than people your age when walking uphill?", Q2 "Do you become short of breath when you climb two flights of stairs at normal pace?", Q3 "Do you become short of breath when walking on flat ground at a normal pace?", and Q4 "Are you short of breath when sitting still?" These questions were included in the Norwegian respiratory questionnaire[20,21] and have been used in Norwegian epidemiologic studies.[17,21] The four questions were combined to a scale (25.7% missing), and cut-off was set at "yes" for Q3 (dyspnoea when walking on flat ground) or Q4 (dyspnoea when sitting still) which approximates dyspnoea grades 2 and 4, respectively, according to the modified British Medical Research Council dyspnoea scale.[22] In the interview the participants were asked "Have you woken at night because you were short of breath in the last 12 months?" Those answering "yes" were classified as woken at night by dyspnoea (0.47% missing).

Lung function

Flow volume spirometry was recorded according to the 1994 ATS recommendations[23] using three pneumotachographs (MasterScope Spirometer version 4.15, Erich Jaeger GmbH, Wuerzburg, Germany).[19] The spirometric measurements and quality control in the Lung study are described in detail elsewhere.[18] Pre-bronchodilator forced vital capacity (FVC) and FEV_1 were obtained, and local

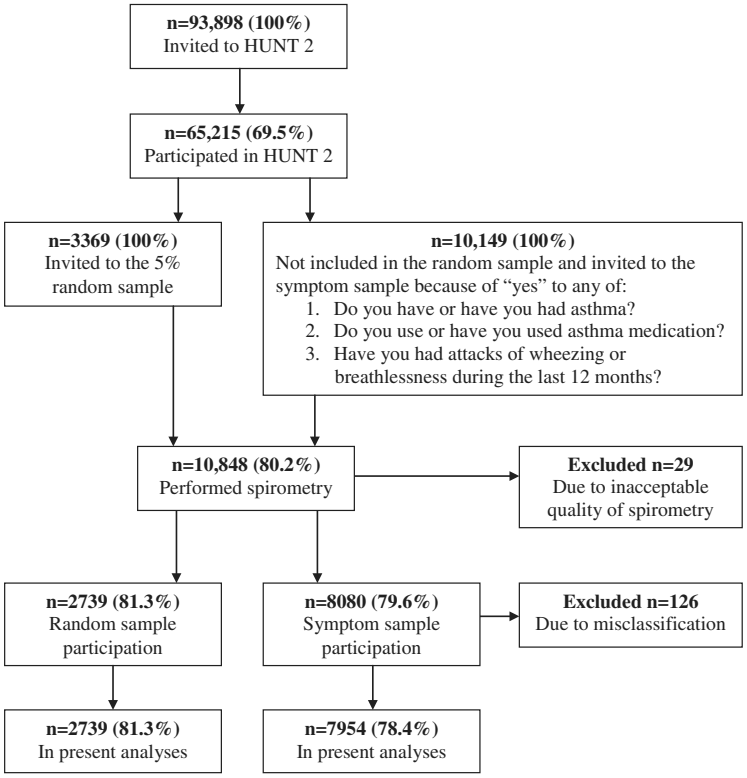

Figure 1 Flow chart of inclusion and exclusion in the Lung study.

prediction equations were used.[18] Lung function was defined in two ways; first percent predicted FEV_1 ($ppFEV_1$) was categorised as $\geq$100.0, 80.0—99.9, 50.0—79.9, and <50.0; then COPD was defined as FEV_1/FVC <70% and categorised according to modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[2] as stage 1 ($ppFEV_1 \geq 80$), stage 2 ($50 \leq ppFEV_1 < 80$), and stage 3 or 4 ($ppFEV_1 < 50$). Normal was defined as $FEV_1/FVC \geq$70% and percent predicted FVC $\geq$80, and those with possible restriction ($FEV_1/FVC \geq$ 70% and percent predicted FVC <80) were excluded from these analyses. In the analysis of the combined association of lung function and anxiety with dyspnoea, the latter two groups of lung function were collapsed to increase statistical power.

Anxiety

A Norwegian translation of the Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety.[24] Although the HADS questionnaire was originally developed to measure anxiety and depression in non-psychiatric patients treated in hospitals, it has also been reported to be valid when used in the general population.[25,26] The HADS consists of 14 questions of which seven measure symptoms of anxiety and seven measure symptoms of depression during the past week. Each question is given a score of 0—3, and the total score for each subscale ranges from 0 to 21. A score of 0—7 indicates normal state, 8—10 borderline state, and 11—21 anxiety state.[26] Psychometric properties of the HADS have been thoroughly tested.[25,27] When one or two answers were missing, the total score was extrapolated by multiplying the sum by 7/6 or 7/5, respectively. In the main analyses anxiety was categorized into three groups; no anxiety (HADS 0—7), borderline (HADS 8—10), and anxiety (HADS 11—21); whereas in the analysis of the combined association of lung function and anxiety, the latter two groups were collapsed into one anxiety symptoms category (HADS 8—21) to increase statistical power. When anxiety was entered as a possible confounder to the association between lung function and dyspnoea, people with missing data on three or more HADS questions (5.92%) were included in a separate category labelled unknown.

Statistical analyses

To enhance the generalizability of our results the regression analyses were weighted to reflect the distribution in the general population. We used an inverse probability weight[28] according to whether the participants were recruited through the symptom or the random sample. A weight of one was assigned to all included through the symptom sample and those in the random sample who fulfilled the inclusion

criteria for the symptom sample. The remaining participants of the random sample were assigned a weight of 20 (as 20 is the inverse of 5%). We also performed sensitivity analyses including subjects from the random sample only.

All analyses were conducted sex specific.[29] Logistic regression was used to compute adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for three separate outcomes; a) dyspnoea when walking on flat ground, b) dyspnoea when sitting still, and c) woken at night by dyspnoea. First, we estimated the adjusted ORs for the three outcomes within levels of lung function ($ppFEV_1$ or COPD stages) using the highest lung function level as reference. Trend tests across $ppFEV_1$ levels were conducted using the sex specific median value within each $ppFEV_1$ level as an ordinal variable in the regression model. Trend tests across COPD stages were conducted using the stages as an ordinal variable. Second, we calculated ORs for the three dyspnoea outcomes associated with anxiety using no anxiety as reference. Linear trend across the anxiety categories was assessed using the categories as an ordinal variable. Third, joint categories of lung function ($ppFEV_1$ or COPD stages) and anxiety were used to estimate the combined association to the three dyspnoea measures using the highest category of lung function without anxiety as the reference category.

All estimated associations were adjusted for potential confounding with age (<40.0, 40.0–49.9, …, ≥80.0), body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown [5.26%]), educational level (<10, 10–12, ≥13 years, unknown [5.63%]), and physical activity (inactive, light activity <1 h per week, light activity 1–2 h per week, light activity ≥3 h per week, only vigorous activity, unknown [11.76%]). Additionally, lung function and anxiety were mutually adjusted when assessing their independent association with the dyspnoea measures. Age and BMI were entered as categorical variables in the regression models to avoid possible residual confounding due to non-linear associations. In separate analyses we additionally adjusted for depression (HADS 0–7, 8–10, 11–21, unknown) when studying the association between anxiety and dyspnoea.

All statistical tests were two-sided using Stata for Windows (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

Ethics

The study was approved by the Regional Committee for Medical Research Ethics (reference 4.2008.59). The Norwegian Data Inspectorate licensed the research register (reference 06/00104-39/CGN).

Results

Baseline characteristics

In general, people with low levels of $ppFEV_1$ were characterised by older age, less education, more inactivity, and a higher proportion was ever smokers (Table 1). Moreover, mean BMI was lowest among those with $ppFEV_1$ <50. The prevalence of anxiety and depression symptoms increased with lower $ppFEV_1$ among women. Baseline characteristics of the subjects among the random, symptom, and weighted samples are presented in Table S1 in the online supplement. The prevalence and mean of key variables did not differ much between the random and the weighted sample.

Lung function in association with dyspnoea

The adjusted ORs for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night

Table 1 Baseline characteristics of the weighted sample in the Lung study according to levels of lung function (weighted $n = 53{,}196$).

	Participants		Age [years]		Body mass index [kg/m^2]		Education ≥13 years		Ever smokers		Inactive		Anxiety symptoms[d]		Depression symptoms[d]	
$ppFEV_1$[a]	*n*	(%)[b]	Mean	(SD)	Mean	(SD)	*n*	(%)[c]	*n*	(%)[c]	*n*	(%)[c]	*n*	(%)[c]	*n*	(%)[c]
Women																
≥100	12,365	(43.0)	49.5	(16.8)	26.0	(3.8)	2666	(22.5)	4917	(42.4)	630	(5.7)	1868	(16.0)	1023	(8.6)
80–99	12,665	(44.0)	48.4	(15.8)	26.4	(4.7)	2439	(20.3)	6226	(51.9)	760	(6.8)	2231	(18.6)	1413	(11.6)
50–79	3481	(12.1)	56.0	(15.6)	26.9	(5.3)	345	(11.3)	2225	(68.8)	331	(11.7)	680	(21.0)	465	(13.9)
<50	277	(1.0)	60.7	(13.9)	24.6	(5.7)	4	(1.7)	191	(72.1)	74	(38.9)	78	(30.8)	63	(24.2)
Men																
≥100	9075	(37.2)	48.3	(15.2)	26.2	(3.1)	1996	(23.1)	4272	(50.3)	367	(4.4)	840	(9.8)	866	(9.9)
80–99	11,634	(47.7)	49.5	(15.7)	26.6	(3.6)	2024	(18.5)	6866	(64.5)	918	(8.7)	1196	(11.0)	1187	(10.8)
50–79	3317	(13.6)	58.8	(15.7)	26.5	(3.6)	371	(12.1)	2501	(77.9)	306	(10.8)	331	(10.6)	321	(10.2)
<50	382	(1.6)	69.9	(9.4)	25.8	(3.9)	13	(3.8)	350	(95.1)	57	(19.4)	31	(8.9)	60	(16.8)

[a] $ppFEV_1$ denotes percent predicted forced expiratory volume in one second.
[b] Percent of total.
[c] Percent within $ppFEV_1$ level, missing excluded.
[d] Anxiety or depression symptoms defined as score 8–21 on the Hospital Anxiety and Depression Scale.

Table 2 Weighted prevalence and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to levels of lung function.

	Women							Men						
		Dyspnoea							Dyspnoea					
ppFEV$_1$[a]	Total	n	(%)[b]	OR[c]	OR[d]	(95% CI)[d]	P$_{trend}$[d]	Total	n	(%)[b]	OR[c]	OR[d]	(95% CI)[d]	P$_{trend}$[d]
	Dyspnoea when walking on flat ground							*Dyspnoea when walking on flat ground*						
≥100	9138	166	(1.8)	1.00	1.00	Reference		6695	129	(1.9)	1.00	1.00	Reference	
80–99	9023	506	(5.6)	3.38	2.80	(1.61 to 4.87)		8311	231	(2.8)	1.39	1.13	(0.52 to 2.44)	
50–79	2691	301	(11.5)	6.75	5.24	(3.04 to 9.03)		2405	274	(11.4)	5.11	4.00	(1.67 to 9.59)	
<50	230	108	(47.0)	43.60	42.98	(17.59 to 105.03)	<0.001	303	164	(54.1)	37.79	38.27	(13.99 to 104.68)	<0.001
	Dyspnoea when sitting still							*Dyspnoea when sitting still*						
≥100	9138	62	(0.7)	1.00	1.00	Reference		6695	53	(0.8)	1.00	1.00	Reference	
80–99	9023	154	(1.7)	2.57	2.23	(0.96 to 5.17)		8311	104	(1.3)	1.54	1.20	(0.52 to 2.80)	
50–79	2691	98	(3.7)	6.17	3.75	(1.44 to 9.77)		2405	92	(3.8)	4.37	2.92	(1.22 to 7.00)	
<50	230	15	(6.5)	10.74	10.41	(3.36 to 32.30)	<0.001	303	27	(8.9)	10.06	7.33	(2.41 to 22.29)	<0.001
	Woken at night by dyspnoea							*Woken at night by dyspnoea*						
≥100	12,301	305	(2.5)	1.00	1.00	Reference		8972	204	(2.3)	1.00	1.00	Reference	
80–99	12,593	566	(4.5)	1.90	1.73	(1.18 to 2.52)		11,626	444	(3.8)	1.73	1.40	(0.82 to 2.38)	
50–79	3477	290	(8.3)	3.66	3.36	(2.18 to 5.17)		3313	298	(9.0)	4.31	4.44	(2.58 to 7.65)	
<50	275	84	(30.5)	17.00	18.27	(8.63 to 38.67)	<0.001	380	113	(29.7)	19.48	19.14	(9.29 to 39.47)	<0.001

[a] ppFEV$_1$ denotes percent predicted forced expiratory volume in one second.
[b] Percentage reporting symptom within each ppFEV$_1$ level.
[c] Adjusted for age (<40.0, 40.0-49.9,..., ≥80.0 years).
[d] Adjusted for age (<40.0, 40.0-49.9,..., ≥80.0 years), anxiety (no anxiety, borderline, anxiety, unknown), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

by dyspnoea increased with lower ppFEV$_1$ (Table 2) or higher COPD stage (Table S2) (all $P_{trend} < 0.002$). Women with ppFEV$_1$ 50–79 had an OR of 5.24 (95% CI 3.04–9.03) for dyspnoea when walking on flat ground compared to women with ppFEV$_1$ ≥100, whereas the corresponding association among men was 4.00 (95% CI 1.67–9.59) (Table 2).

Anxiety in association with dyspnoea

The adjusted ORs for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea increased with increasing anxiety symptoms (all $P_{trend} < 0.001$) (Table 3). Women with anxiety (HADS 11–21) had an OR of 3.39 (95% CI 1.95–5.88) for dyspnoea when walking on flat ground compared to women without anxiety (HADS 0–7), whereas the corresponding association among men was 3.88 (95% CI 1.77–8.50).

In general, having anxiety symptoms increased the adjusted ORs for reporting dyspnoea within ppFEV$_1$ levels (Table 4) or COPD stages (Table S3). This trend was most evident when lung function was measured as ppFEV$_1$. Compared to women with ppFEV$_1$ ≥100 without anxiety (HADS 0–7), women with ppFEV$_1$ 80–99 without anxiety had an OR of 2.46 (95% CI 1.25–4.83) for dyspnoea when walking on flat ground, whereas women with ppFEV$_1$ 80–99 with anxiety symptoms (HADS 8–21) had an OR of 7.71 (95% CI 3.65–16.28) for the same outcome (Table 4). The corresponding associations among men were 1.10 (95% CI 0.44–2.73) and 5.17 (95% CI 1.88–14.24), respectively. Further adjustments for depression did not change the results (data not shown).

Sensitivity analyses

In general, the results from the analyses restricted to the random sample were comparable to the results from the weighted analyses of the total sample (Tables S4–S6). However, the estimates were imprecise due to few participants in the random sample.

Discussion

In this cross-sectional study from a general population, we found lung function and anxiety to be independently associated with dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea. Within lung function levels, reporting dyspnoea was more common among people with anxiety symptoms than among people without.

Lung function in association with dyspnoea

Another cross-sectional study from the general population has also found an association between airflow limitation and dyspnoea.[30] In-line with this, dyspnoea has been found to discriminate between people with and without bronchial obstruction.[31]

The association between lung function and dyspnoea in people with asthma and COPD is not consistent. Weak correlations have been found between FEV$_1$ and asthma symptoms in asthma patients in general practice,[12] and between FEV$_1$ and dyspnoea in patients with COPD.[8] On the

Table 3 Weighted prevalence and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to levels of anxiety.

	Women							Men						
		Dyspnoea							Dyspnoea					
Anxiety[a]	Total	*n*	(%)[b]	OR[c]	OR[d]	(95% CI)[d]	P_{trend}[d]	Total	*n*	(%)[b]	OR[c]	OR[d]	(95% CI)[d]	P_{trend}[d]
	Dyspnoea when walking on flat ground							*Dyspnoea when walking on flat ground*						
No anxiety	16,286	632	(3.9)	1.00	1.00	Reference		15,432	597	(3.9)	1.00	1.00	Reference	
Borderline	2443	222	(9.1)	2.49	2.27	(1.32 to 3.93)		1100	102	(9.3)	3.46	4.00	(1.93 to 8.27)	
Anxiety	1299	176	(13.5)	4.10	3.39	(1.95 to 5.88)	<0.001	565	65	(11.5)	4.50	3.88	(1.77 to 8.50)	<0.001
	Dyspnoea when sitting still							*Dyspnoea when sitting still*						
No anxiety	16,286	176	(1.1)	1.00	1.00	Reference		15,432	206	(1.3)	1.00	1.00	Reference	
Borderline	2443	60	(2.5)	2.19	2.00	(0.94 to 4.23)		1100	35	(3.2)	2.85	2.75	(1.57 to 4.82)	
Anxiety	1299	85	(6.5)	6.12	4.86	(2.23 to 10.59)	<0.001	565	26	(4.6)	4.08	3.64	(2.05 to 6.47)	<0.001
	Woken at night by dyspnoea							*Woken at night by dyspnoea*						
No anxiety	22,176	755	(3.4)	1.00	1.00	Reference		20,493	786	(3.8)	1.00	1.00	Reference	
Borderline	3160	240	(7.6)	2.38	2.11	(1.30 to 3.43)		1604	101	(6.3)	1.79	1.70	(1.19 to 2.44)	
Anxiety	1672	148	(8.9)	2.73	2.40	(1.49 to 3.86)	<0.001	773	66	(8.5)	2.57	2.34	(1.47 to 3.72)	<0.001

[a] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0–7, borderline = HADS 8–10, and anxiety = HADS 11–21.
[b] Percentage reporting symptom within each anxiety level.
[c] Adjusted for age (<40.0, 40.0–49.9,..., ≥80.0 years).
[d] Adjusted for age (<40.0, 40.0–49.9,..., ≥80.0 years), ppFEV$_1$ (≥100.0, 80.0–99.9, 50.0–79.9, and <50.0), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10–12, ≥13 years, unknown), and physical activity (inactive, light activity <1 h per week, light activity 1–2 h per week, light activity ≥3 h per week, only vigorous activity, unknown).

Table 4 Weighted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to joint categories of lung function and anxiety.

	Women										Men									
	No anxiety[a]					Anxiety symptoms[a]					No anxiety[a]					Anxiety symptoms[a]				
		Dyspnoea					Dyspnoea					Dyspnoea					Dyspnoea			
$ppFEV_1$[b]	Total	*n*	(%)[c]	OR[d]	(95% CI)[d]	Total	*n*	(%)[c]	OR[d]	(95% CI)[d]	Total	*n*	(%)[c]	OR[d]	(95% CI)[d]	Total	*n*	(%)[d]	OR[d]	(95% CI)[d]
	Dyspnoea when walking on flat ground										*Dyspnoea when walking on flat ground*									
≥100	7274	109	(1.5)	1.00	Reference	1428	47	(3.3)	1.99	(0.68 to 5.84)	5936	96	(1.6)	1.00	Reference	604	30	(5.0)	4.46	(0.86 to 23.19)
80–99	6973	284	(4.1)	2.46	(1.25 to 4.83)	1677	205	(12.2)	7.71	(3.65 to 16.28)	7185	158	(2.2)	1.10	(0.44 to 2.73)	804	66	(8.2)	5.17	(1.88 to 14.24)
<80	2039	239	(11.7)	6.23	(3.45 to 11.28)	637	146	(22.9)	15.14	(7.13 to 32.12)	2311	343	(14.8)	5.75	(2.23 to 14.81)	257	71	(27.6)	15.19	(4.74 to 48.64)
	Dyspnoea when sitting still										*Dyspnoea when sitting still*									
≥100	7274	27	(0.4)	1.00	Reference	1428	35	(2.5)	6.08	(1.82 to 20.30)	5936	42	(0.7)	1.00	Reference	604	8	(1.3)	2.11	(0.58 to 7.64)
80–99	6973	97	(1.4)	3.40	(1.68 to 6.87)	1677	52	(3.1)	7.31	(3.28 to 16.29)	7185	72	(1.0)	1.12	(0.37 to 3.33)	804	30	(3.7)	4.33	(1.50 to 12.47)
<80	2039	52	(2.6)	5.78	(3.05 to 10.97)	637	58	(9.1)	17.81	(6.32 to 50.13)	2311	92	(4.0)	3.30	(1.17 to 9.30)	257	23	(8.9)	8.92	(2.47 to 32.21)
	Woken at night by dyspnoea										*Woken at night by dyspnoea*									
≥100	9734	182	(1.9)	1.00	Reference	1868	112	(6.0)	3.29	(1.59 to 6.78)	7682	170	(2.2)	1.00	Reference	819	27	(3.3)	1.61	(0.81 to 3.20)
80–99	9719	320	(3.3)	1.64	(1.08 to 2.50)	2206	183	(8.3)	4.23	(2.41 to 7.44)	9711	303	(3.1)	1.39	(0.76 to 2.57)	1196	72	(6.0)	2.79	(1.44 to 5.41)
<80	2723	253	(9.3)	5.33	(3.31 to 8.60)	758	93	(12.3)	6.45	(3.70 to 11.25)	3100	131	(10.1)	5.04	(2.75 to 9.24)	362	68	(18.8)	9.71	(4.18 to 19.61)

[a] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0–7, anxiety symptoms = HADS 8–21.

[b] $ppFEV_1$ denotes percent predicted forced expiratory volume in one second.

[c] Percentage reporting symptom within each combined category of lung function and anxiety.

[d] Adjusted for age (<40.0, 40.0–49.9,… ≥80.0 years), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10–12, ≥13 years, unknown), and physical activity (inactive, light activity <1 h per week, light activity 1–2 h per week, light activity ≥3 h per week, only vigorous activity, unknown).

other hand, Schlecht et al.[32] found a clear association between low FEV_1 and severe dyspnoea in people with COPD. These inconsistent findings may be due to the limited ability of FEV_1 to reflect hyperinflation. Hyperinflation is one of the main causes of dyspnoea in people with obstructive lung diseases.[8]

Dyspnoea may also be a result of abnormalities in respiratory muscles, blood-gases, ventilatory impedance, breathing patterns, or inability to adapt to heightened ventilatory demands.[9] FEV_1 does not necessarily reflect this.

Anxiety in association with dyspnoea

A few other studies have used data from the general population when studying the influence of psychological status on respiratory symptom reporting taking lung function into account.[11,13,16] When studying 600 "healthy" never-smokers between 14 and 55 years of age without any respiratory or other major diseases and with normal lung function, Dales et al.[13] found a strong positive association between anxiety and dyspnoea. This was supported by Janson et al.[16] who also found a clear association between anxiety and dyspnoea in a cross-sectional epidemiologic study. In their review from 2005 Chetta et al.[15] concluded that subjects with more psychological symptoms are more likely to report respiratory symptoms.

Similar associations have also been found among people with asthma and COPD.[10,12] Among patients with asthma in general practice, anxiety has been found to help explain symptoms more than lung function and asthma severity.[12] Also Giardino et al.[10] found an association between anxiety and shortness of breath after adjusting for lung function in patients with emphysema.

The cause-and-effect relationships between anxiety and dyspnoea are unclear.[9] Bailey suggests that dyspnoea may cause anxiety, and anxiety may cause further dyspnoea, and she refers to this as a dyspnoea—anxiety—dyspnoea cycle.[33] However, findings from a prospective population-based study suggest that psychological symptoms like anxiety may cause dyspnoea.[11] In people with COPD, anxiety may cause dyspnoea by increasing respiratory rate and thereby reducing expiration time leading to worse hyperinflation.[8] Since we controlled for $ppFEV_1$ in our models, it is unlikely that the observed association between anxiety and dyspnoea could be explained by differences in $ppFEV_1$.

Although we found anxiety symptoms to be associated with reporting dyspnoea in three different situations, the cause-and-effect relationship between anxiety and dyspnoea may differ depending on the situation in which dyspnoea is experienced. One might suspect that anxiety could cause dyspnoea when sitting still, and that experiencing dyspnoea when walking on flat ground or waking up with dyspnoea could cause anxiety. However, the current cross-sectional study cannot confirm these speculations, and this needs to be further studied in other study designs.

To distinguish anxiety and depression, which often coexist,[34] we adjusted for depression in separate analyses. Since this did not change our results, it is unlikely that depression may explain the observed associations.

Our results indicate that, in addition to lung function, anxiety may explain some of the variation in reported dyspnoea. However, whether anxiety causes dyspnoea or dyspnoea causes anxiety cannot be answered by the current study. An alternative explanation of our findings may be that the perception of dyspnoea differs among those with and without anxiety. Thus, anxiety may affect the reporting of dyspnoea. Still, when handling patients with obstructive lung diseases, treatment of both airway obstruction and anxiety, if present, are important in order to reduce the total symptom burden.

Methodological considerations

Due to the cross-sectional study design, we cannot draw conclusions about cause-and-effect relationships.[35] However, it is plausible to assume that reduced lung function or the condition causing it may cause dyspnoea, and not the other way around. Such assumptions cannot be drawn about the association between anxiety and dyspnoea as explained above. Further research on this topic should therefore be carried out in prospective study designs.

To overcome possible selection bias due to recruitment of subjects through the symptom or the random sample, we weighted the participants according to sample origin to imitate the characteristic properties of all participants in HUNT 2. Sensitivity analyses restricted to the random sample were comparable to the results of the weighted analyses though the small sample size gave imprecise results. In addition, the prevalence and mean of key variables in the weighted sample were very close to those in the random sample.

We studied lung function and anxiety in association with dyspnoea through the total range of lung function independent of possible diagnoses. However, in the supplementary analyses of COPD stages, 30% of people without COPD may have been misclassified as having COPD due to the use of pre-bronchodilator measurements.[36]

Our study is one of few population-based studies assessing lung function and anxiety in association with dyspnoea. A major strength of our study is the large sample size with a wide age span. The response rate was relatively high. A non-responder study did not indicate serious selection bias.[37] We believe our results are valid for the general population of Norway and other comparable countries.

Conclusion

Impaired lung function and anxiety symptoms were independently associated with reporting dyspnoea. Within lung function levels, reporting dyspnoea was more common among people with anxiety symptoms than among people without. This suggests that, in addition to its relation to reduced lung function, the subjective experience of breathing discomfort may also influence or be influenced by anxiety.

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Contributorship statement

LL and AL planned the study and are guarantors of this paper. LL analysed the data and wrote the paper. TILN supervised the analyses. All authors interpreted the results and revised the paper. As project leader for the HUNT 2 Lung study, AL was responsible for planning, data collection, and quality assurance of data in the Lung study.

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Conflict of interest statement

There are no conflicts of interest.

Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2012.03.017.

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Table S1: Self-reported respiratory symptoms and medical diagnoses, lung function, anxiety, and other characteristics among subjects in the symptom, random, and weighted sample

	Women						Men					
	Symptom n=4143, 52.1%[a]		Random n=1484, 54.2%[a]		Weighted n=28 788, 54.1%[a]		Symptom n=3811, 47.9%[a]		Random n=1255, 45.8%[a]		Weighted n=24 408, 45.9%[a]	
Respiratory symptoms, n (%)[b]												
Attacks of wheezing or breathlessness	3165	(76.4)	215	(14.5)	3380	(11.7)	2879	(75.6)	179	(14.3)	3058	(12.5)
Ever had asthma	2362	(57.3)	140	(9.4)	2502	(8.7)	2113	(55.8)	113	(9.0)	2226	(9.1)
Ever used asthma medication	2284	(55.3)	127	(8.6)	2411	(8.4)	1849	(48.7)	101	(8.1)	1950	(8.0)
Medical diagnoses (ever had), n (%)[b]												
Myocardial infarction	97	(2.4)	19	(1.3)	344	(1.2)	266	(7.0)	65	(5.3)	1281	(5.3)
Angina pectoris	252	(6.1)	39	(2.6)	785	(2.7)	367	(9.7)	62	(5.1)	1265	(5.3)
Stroke or cerebral haemorrhage	87	(2.1)	27	(1.8)	475	(1.7)	95	(2.5)	21	(1.7)	439	(1.8)
Diabetes mellitus	139	(3.4)	45	(3.1)	773	(2.7)	152	(4.0)	27	(2.2)	578	(2.4)
Asthma	1538	(51.4)	96	(8.9)	1653	(8.0)	1353	(48.6)	76	(8.3)	1467	(8.4)
Chronic bronchitis or emphysema	498	(16.9)	34	(3.2)	703	(3.4)	541	(19.7)	50	(5.5)	876	(5.0)
Lung function, mean (SD)												
FEV_1[c] [L]	2.6	(0.8)	2.8	(0.7)	2.8	(0.7)	3.4	(1.1)	3.8	(1.0)	3.8	(1.0)
$ppFEV_1$[d]	88.7	(19.0)	96.7	(16.0)	96.6	(16.4)	84.7	(20.6)	94.5	(16.1)	94.5	(16.4)
FVC[e]	3.3	(0.8)	3.5	(0.8)	3.5	(0.8)	4.6	(1.2)	4.9	(1.0)	4.9	(1.0)
FEV_1/FVC [%]	76.6	(10.3)	80.0	(7.1)	79.9	(7.4)	72.5	(11.8)	76.9	(8.6)	76.9	(8.7)
Anxiety[f], n (%)[b]												
No anxiety	2880	(73.8)	1152	(82.5)	22 291	(82.1)	2911	(81.0)	1052	(89.7)	20 588	(89.6)
Borderline	611	(15.7)	160	(11.5)	3184	(11.7)	437	(12.2)	85	(7.3)	1624	(7.1)
Anxiety	410	(10.5)	85	(6.1)	1673	(6.2)	244	(6.8)	36	(3.1)	774	(3.4)
Other, mean (SD)												
Age [years]	50.4	(17.1)	49.9	(16.5)	49.9	(16.4)	51.9	(16.9)	50.6	(16.0)	50.7	(16.0)
Body mass index [kg/m^2]	27.2	(5.2)	26.3	(4.4)	26.3	(4.4)	27.0	(3.9)	26.5	(3.4)	26.4	(3.4)
Other, n (%)[b]												
Education ≥13 years	654	(16.8)	278	(19.9)	5454	(20.1)	569	(15.7)	225	(19.1)	4404	(19.2)
Ever smoker	2303	(58.8)	711	(51.0)	13 559	(50.1)	2620	(71.6)	710	(61.2)	13 989	(61.6)
Inactive	373	(10.4)	92	(7.0)	1795	(7.1)	327	(9.6)	86	(7.6)	1648	(7.5)
Depression[g]	610	(15.3)	150	(10.5)	2964	(10.7)	642	(17.5)	120	(10.1)	2434	(10.5)

[a] Percent within each sample. [b] Percent within variable, sample, and sex, missing excluded. [c] FEV_1 = Forced expiratory volume in one second. [d] $ppFEV_1$ = Percent predicted FEV_1. [e] FVC = Forced vital capacity. [f] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0-7, borderline = HADS 8-10, and anxiety = HADS 11-21. [g] Depression = HADS 8-21.

Table S2: Weighted prevalence and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to COPD stages

	Women							*Men*						
		Dyspnoea							Dyspnoea					
COPD[a]	**Total**	**n**	**(%)[b]**	**OR[c]**	**OR[d]**	**(95% CI)[d]**	**P_{trend}[d]**	**Total**	**n**	**(%)[b]**	**OR[c]**	**OR[d]**	**(95% CI)[d]**	**P_{trend}[d]**
	Dyspnoea when walking on flat ground							***Dyspnoea when walking on flat ground***						
Normal	18 058	656	(3.6)	1.00	1.00	Reference		14 041	347	(2.5)	1.00	1.00	Reference	
Stage 1	503	17	(3.4)	0.84	0.97	(0.41 to 2.29)		1160	27	(2.3)	0.77	0.79	(0.41 to 1.55)	
Stage 2	1131	166	(14.7)	4.30	3.57	(2.00 to 6.42)		1505	171	(11.4)	3.77	3.33	(1.51 to 7.35)	
Stage 3-4	225	105	(46.7)	21.76	22.70	(10.25 to 50.25)	<0.001	276	160	(58.0)	35.70	40.36	(18.85 to 86.42)	<0.001
	Dyspnoea when sitting still							***Dyspnoea when sitting still***						
Normal	18 058	218	(1.2)	1.00	1.00	Reference		14 041	149	(1.0)	1.00	1.00	Reference	
Stage 1	503	10	(2.0)	1.56	1.37	(0.45 to 4.24)		1160	15	(1.3)	1.04	1.06	(0.47 to 2.40)	
Stage 2	1131	64	(5.7)	5.47	3.54	(1.38 to 9.06)		1505	68	(4.5)	3.82	3.27	(1.54 to 6.93)	
Stage 3-4	225	15	(6.7)	6.23	6.53	(2.73 to 15.61)	0.001	276	24	(8.7)	6.33	6.76	(2.77 to 16.49)	<0.001
	Woken at night by dyspnoea							***Woken at night by dyspnoea***						
Normal	24 610	884	(3.6)	1.00	1.00	Reference		19 457	624	(3.2)	1.00	1.00	Reference	
Stage 1	803	30	(3.7)	1.03	1.29	(0.72 to 2.32)		1455	46	(3.2)	0.99	1.30	(0.83 to 2.04)	
Stage 2	1552	151	(9.7)	2.94	2.87	(1.91 to 4.32)		2086	201	(9.6)	3.26	4.18	(2.68 to 6.50)	
Stage 3-4	270	83	(30.7)	11.77	12.68	(6.50 to 24.73)	<0.001	332	111	(33.4)	16.38	20.78	(12.16 to 35.51)	<0.001

[a] COPD denotes Chronic Obstructive Pulmonary Disease (Normal = Forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC)≥70% and percent predicted FVC≥80, COPD stage 1 = FEV_1/FVC<70% and $ppFEV_1$≥80, COPD stage 2 = FEV_1/FVC<70% and 50≤$ppFEV_1$<80, COPD stage 3 or 4 = FEV_1/FVC<70% and $ppFEV_1$<50). [b] Percentage reporting symptom within each $ppFEV_1$ level. [c] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years). [d] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years), anxiety (no anxiety, borderline, anxiety, unknown), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

Table S3: Weighted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to joint categories of COPD and anxiety

	Women										*Men*									
	No anxiety[a]					Anxiety symptoms[a]					No anxiety[a]					Anxiety symptoms[a]				
	Dyspnoea					Dyspnoea					Dyspnoea					Dyspnoea				
COPD[b]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[d]	OR[d]	(95% CI)[d]
	Dyspnoea when walking on flat ground										***Dyspnoea when walking on flat ground***									
Normal	14 090	372	(2.6)	1.00	Reference	3151	258	(8.2)	3.01	(1.76 to 5.12)	12 330	242	(2.0)	1.00	Reference	1318	95	(7.2)	4.53	(2.10 to 9.76)
Stage 1	372	12	(3.2)	1.47	(0.60 to 3.60)	86	3	(3.5)	1.05	(0.19 to 5.66)	966	21	(2.2)	0.85	(0.40 to 1.84)	109	6	(5.5)	2.91	(0.76 to 11.19)
Stage 2-4	974	162	(16.6)	5.82	(3.08 to 10.98)	331	93	(28.1)	11.50	(4.74 to 27.88)	1503	282	(18.8)	6.42	(2.94 to 14.01)	150	31	(20.7)	8.10	(2.95 to 22.27)
	Dyspnoea when sitting still										***Dyspnoea when sitting still***									
Normal	14 090	122	(0.9)	1.00	Reference	3151	90	(2.9)	2.11	(0.58 to 7.64)	12 330	105	(0.9)	1.00	Reference	1318	39	(3.0)	3.20	(1.59 to 6.45)
Stage 1	372	7	(1.9)	1.12	(0.37 to 3.33)	86	2	(2.3)	4.33	(1.50 to 12.47)	966	11	(1.1)	1.85	(0.57 to 6.04)	109	4	(3.7)	2.59	(0.40 to 16.74)
Stage 2-4	974	35	(3.6)	3.30	(1.17 to 9.30)	331	43	(13.0)	8.92	(2.47 to 32.21)	1503	77	(5.1)	3.85	(1.64 to 9.02)	150	12	(8.0)	13.71	(3.84 to 48.92)
	Woken at night by dyspnoea										***Woken at night by dyspnoea***									
Normal	19 176	510	(2.7)	1.00	Reference	4126	300	(7.3)	2.81	(1.82 to 4.32)	16 459	456	(2.8)	1.00	Reference	1917	92	(4.8)	1.78	(1.17 to 2.69)
Stage 1	596	23	(3.9)	2.17	(1.21 to 3.90)	118	7	(5.9)	2.53	(0.81 to 7.95)	1199	33	(2.8)	1.15	(0.69 to 1.92)	124	12	(9.7)	5.86	(2.28 to 15.04)
Stage 2-4	1279	154	(12.0)	6.06	(4.02 to 9.13)	349	57	(16.3)	5.02	(2.55 to 9.86)	1997	243	(12.2)	5.28	(3.33 to 8.38)	239	45	(18.8)	8.99	(4.73 to 17.11)

[a] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0-7, anxiety symptoms = HADS 8-21. [b] COPD denotes Chronic Obstructive Pulmonary Disease (Normal = Forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC)≥70% and percent predicted FVC≥80, COPD stage 1 = FEV_1/FVC<70% and $ppFEV_1$≥80, COPD stage 2 = FEV_1/FVC<70% and 50≤$ppFEV_1$<80, COPD stage 3 or 4 = FEV_1/FVC<70% and $ppFEV_1$<50)). [c] Percentage reporting symptom within each combined category of lung function and anxiety. [d] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

Table S4 Prevalence and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to levels of lung function among participants in the random sample (n=2739)

	Women							*Men*						
		Dyspnoea							Dyspnoea					
ppFEV$_1$[a]	**Total**	**n**	**(%)**[b]	**OR**[c]	**OR**[d]	**(95% CI)**[d]	**P$_{trend}$**[d]	**Total**	**n**	**(%)**[b]	**OR**[c]	**OR**[d]	**(95% CI)**[d]	**P$_{trend}$**[d]
	Dyspnoea when walking on flat ground							***Dyspnoea when walking on flat ground***						
≥100	473	8	(1.7)	1.00	1.00	Reference		342	9	(2.6)	1.00	1.00	Reference	
80-99	472	28	(5.9)	3.85	2.91	(1.26 to 6.72)		446	11	(2.5)	0.91	0.63	(0.23 to 1.71)	
50-79	136	16	(11.8)	7.20	4.44	(1.69 to 11.65)		120	15	(12.5)	4.23	3.90	(1.30 to 11.71)	
<50	12	7	(58.3)	62.20	39.88	(7.03 to 226.41)	<0.001	16	7	(43.8)	17.89	22.33	(4.12 to 121.08)	<0.001
	Dyspnoea when sitting still							***Dyspnoea when sitting still***						
≥100	473	2	(0.4)	1.00	1.00	Reference		342	3	(0.9)	1.00	1.00	Reference	
80-99	472	10	(2.1)	5.14	3.83	(0.74 to 19.92)		446	4	(0.9)	1.05	0.79	(0.13 to 4.90)	
50-79	136	5	(3.7)	8.34	2.36	(0.34 to 16.44)		120	4	(3.3)	4.12	2.27	(0.25 to 20.82)	
<50	12	1	(8.3)	19.10	27.96	(1.27 to 615.51)	0.124	16	0	(0.0)	-	-	(-)	0.765
	Woken at night by dyspnoea							***Woken at night by dyspnoea***						
≥100	635	15	(2.4)	1.00	1.00	Reference		455	17	(3.7)	1.00	1.00	Reference	
80-99	653	38	(5.8)	2.64	2.47	(1.32 to 4.60)		609	30	(4.9)	1.38	1.11	(0.58 to 2.13)	
50-79	175	16	(9.1)	4.33	4.02	(1.83 to 8.85)		168	13	(7.7)	2.31	1.96	(0.83 to 4.62)	
<50	14	1	(7.1)	3.20	4.05	(0.41 to 39.79)	<0.001	18	5	(27.8)	12.50	8.29	(2.12 to 32.48)	0.006

[a] ppFEV$_1$ denotes percent predicted forced expiratory volume in one second. [b] Percentage reporting symptom within each ppFEV$_1$ level. [c] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years). [d] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years), anxiety (no anxiety, borderline, anxiety, unknown), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

Table S5: Prevalence and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to levels of anxiety among participants in the random sample (n=2739)

	Women							*Men*						
		Dyspnoea							Dyspnoea					
Anxiety[a]	**Total**	**n**	**(%)**[b]	**OR**[c]	**OR**[d]	**(95% CI)**[d]	**P_{trend}**[d]	**Total**	**n**	**(%)**[b]	**OR**[c]	**OR**[d]	**(95% CI)**[d]	**P_{trend}**[d]
	Dyspnoea when walking on flat ground							***Dyspnoea when walking on flat ground***						
No anxiety	849	33	(3.9)	1.00	1.00	Reference		800	32	(4.0)	1.00	1.00	Reference	
Borderline	126	13	(10.3)	3.12	3.21	(1.47 to 7.04)		61	6	(9.8)	4.15	4.67	(1.42 to 15.30)	
Anxiety	68	10	(14.7)	5.04	4.42	(1.84 to 10.64)	<0.001	28	3	(10.7)	5.23	6.83	(1.46 to 32.02)	0.001
	Dyspnoea when sitting still							***Dyspnoea when sitting still***						
No anxiety	849	6	(0.7)	1.00	1.00	Reference		800	7	(0.9)	1.00	1.00	Reference	
Borderline	126	6	(4.8)	7.48	10.46	(2.53 to 43.34)		61	2	(3.3)	5.58	3.91	(0.53 to 29.05)	
Anxiety	68	5	(7.4)	12.23	16.34	(3.50 to 76.19)	<0.001	28	2	(7.1)	14.33	12.72	(1.42 to 113.65)	0.012
	Woken at night by dyspnoea							***Woken at night by dyspnoea***						
No anxiety	1146	48	(4.2)	1.00	1.00	Reference		1048	47	(4.5)	1.00	1.00	Reference	
Borderline	159	10	(6.3)	1.56	1.28	(0.61 to 2.68)		84	4	(4.8)	1.13	1.00	(0.34 to 2.93)	
Anxiety	85	5	(5.9)	1.42	1.09	(0.40 to 2.94)	0.646	36	5	(13.9)	3.94	4.18	(1.47 to 11.87)	0.031

[a] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0-7, borderline = HADS 8-10, and anxiety = HADS 11-21. [b] Percentage reporting symptom within each anxiety level. [c] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years). [d] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years), $ppFEV_1$ (≥100.0, 80.0–99.9, 50.0–79.9, and <50.0), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

Table S6: Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for reporting dyspnoea when walking on flat ground, dyspnoea when sitting still, and woken at night by dyspnoea according to joint categories of lung function and anxiety among participants in the random sample (n=2739)

	Women										*Men*									
	No anxiety[a]					Anxiety symptoms[a]					No anxiety[a]					Anxiety symptoms[a]				
		Dyspnoea					Dyspnoea					Dyspnoea					Dyspnoea			
ppFEV$_1$[b]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[c]	OR[d]	(95% CI)[d]	Total	n	(%)[c]	OR[d]	(95% CI)[d]
	Dyspnoea when walking on flat ground										***Dyspnoea when walking on flat ground***									
≥100	377	6	(1.6)	1.00	Reference	74	2	(2.7)	1.71	(0.32 to 9.02)	300	7	(2.3)	1.00	Reference	34	2	(5.9)	4.82	(0.82 to 28.14)
80-99	365	14	(3.8)	1.88	(0.67 to 5.26)	86	12	(14.0)	9.20	(3.10 to 27.28)	384	6	(1.6)	0.49	(0.15 to 1.58)	43	4	(9.3)	3.61	(0.79 to 16.54)
<80	107	13	(12.2)	4.17	(1.36 to 12.79)	34	9	(26.5)	16.19	(4.73 to 55.35)	116	19	(16.4)	4.64	(1.49 to 14.44)	12	3	(25.0)	18.22	(2.35 to 141.39)
	Dyspnoea when sitting still										***Dyspnoea when sitting still***									
≥100	377	0	(0.0)	1.00	Reference	74	2	(2.7)	1.00	Reference	300	2	(0.7)	1.00	Reference	34	1	(2.9)	6.38	(0.39 to 104.17)
80-99	365	5	(1.4)	-	(-)	86	4	(4.7)	-	(-)	384	2	(0.5)	0.58	(0.07 to 4.82)	43	2	(4.7)	5.60	(0.53 to 59.79)
<80	107	1	(0.9)	-	(-)	34	5	(14.7)	-	(-)	116	3	(2.6)	2.37	(0.22 to 25.42)	12	1	(8.3)	8.45	(0.31 to 227.50)
	Woken at night by dyspnoea										***Woken at night by dyspnoea***									
≥100	506	12	(2.4)	1.00	Reference	93	3	(3.2)	1.27	(0.34 to 4.73)	385	15	(3.9)	1.00	Reference	43	1	(2.3)	0.59	(0.07 to 4.67)
80-99	502	24	(4.8)	1.99	(0.97 to 4.08)	112	7	(6.3)	2.26	(0.84 to 6.13)	509	21	(4.1)	0.99	(0.50 to 1.97)	60	5	(8.3)	1.98	(0.66 to 5.92)
<80	138	12	(8.7)	4.01	(1.64 to 9.76)	39	5	(12.8)	5.35	(1.61 to 17.78)	154	11	(7.1)	1.51	(0.61 to 3.72)	17	3	(17.7)	5.01	(1.20 to 20.89)

[a] Anxiety measured by the Hospital Anxiety and Depression Scale (HADS): No anxiety = HADS 0-7, anxiety symptoms = HADS 8-21. [b] ppFEV1 denotes percent predicted forced expiratory volume in one second. [c] Percentage reporting symptom within each combined category of lung function and anxiety. [d] Adjusted for age (<40.0, 40.0-49.9,…, ≥80.0 years), body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), smoking history (never smoker, former smoker and <15 pack-years, former smoker and ≥15 pack-years, current smoker and <15 pack-years, current smoker and ≥15 pack-years, unknown), educational level (<10, 10-12, ≥13 years, unknown), and physical activity (inactive, light activity <1 hours per week, light activity 1-2 hours per week, light activity ≥3 hours per week, only vigorous activity, unknown).

Paper II

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Paper III

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