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Chronic obstructive pulmonary disease in Norway; prevalence, classification, hospitalization, and mortality

The HUNT Lung Study

Thesis for the degree of Philosophiae Doctor

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To my Family and Son (Saarav)

Kronisk obstruktiv lungesykdom i Norge; forekomst, klassifisering, sykehusinnleggelser og dødelighet

Lungeprosjektet i Helseundersøkelsene i Nord-Trøndelag (HUNT)

Kronisk obstruktiv lungesykdom (kols) er en vanlig lungesykdom, og sykdommen er rangert som verdens tredje hyppigste dødsårsak. De vanligste symptomene ved kols er tung pust, kronisk hoste, oppspytt og pipende pust. Pga. endringer i alderssammensetning, luftforurensing og røykevaner må beregninger av forekomst av kols stadig oppdateres. Kols kan ikke kureres, men god diagnostikk og behandling kan redusere symptomer, bedre livskvaliteten og redusere risiko for alvorlige forverrelser og død. Den internasjonale komiteen The Global Initiative for Chronic Obstructive Lung Disease (GOLD) har anbefalt post- bronkodilator (BD) spirometri for å diagnostisere og klassifisere kols, men hvorvidt dette er beste prognostiske mål sammenlignet med f. eks. pre-BD er ikke sikkert dokumentert. I 2017 oppdaterte GOLD klassifiseringen av kols for tredje gang uten et at det forelå et vitenskapelig grunnlag for dets anvendbarhet mht. å guide behandling og vurdere prognose. Nyere forskning peker på at alternative mål på lungefunksjon bør vurderes for klassifisering av alvorlighetsgrad ved kols. Derfor er videre forskning blant ulike populasjoner nødvendig.

For å imøtekomme behovet for fremtidig forskning på forekomst, diagnose og klassifisering av kols brukte vi grunnlagsdata fra Helseundersøkelsen i Nord-Trøndelag (HUNT) og oppfølgingsdata fra Dødsårsaksregisteret og fra Helse Nord-Trøndelag (HNT) for å studere 1) forekomsten av kols i perioden 1995-1997 og 2006-2008; 2) de diskriminerende egenskapene til pre-BD versus post-BD lungefunksjon til å predikere dødelighet; 3) GOLD- klassifiseringenes diskriminerende egenskaper til å predikere mortalitet og sykehusinnleggelser og 4) diskriminerende egenskaper til et vanlig brukte lungefunksjonsmål mht. å predikere mortalitet og sykehusinnleggelser.

Vi fant at forekomsten av kols blant menn falt fra 1995-1997 til 2006-2008 mens forekomsten hos kvinner var relativt stabil. Post-BD lungefunksjon predikerte dødelighet litt bedre enn pre-BD. Vi registrerte at GOLD 2017 sin klassifikasjon generelt hadde dårlig prognostisk verdi mht. dødelighet og kolsrelaterte sykehusinnleggelser. Vår studie fant at alternative mål på lungefunksjon, som er uavhengig av referanseverdier slik som FEV_1Q, generelt var bedre til å predikere dødelighet og kolsrelaterte sykehusinnleggelser sammenlignet med et stort antall vanlig brukte lungefunksjonsmål og klassifiseringer.

Denne avhandlingen gir estimat på forekomst av kols og endringer av denne i Nord-Trøndelag og bidrar dermed til å øke vår kunnskap om sykdommen. Videre utredes alternative mål på lungefunksjon som FEV_1Q for bedre klassifisering av alvorlighetsgrad ved kols. Forskningsresultatene kan være til hjelp ved prioritering og planlegging av offentlige helsetiltak, som veiledning av behandling for å bedre prognose, og i innsatsen for å forebygge utvikling av kols

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List of papers

This thesis is based on the following papers:

Paper I.

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Paper II.

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Paper III.

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Paper IV.

Bhatta L, Leivseth L, Mai XM, Henriksen AH, Carslake D, Chen Y, Langhammer A, Brumpton BM. Spirometric classifications of COPD severity, mortality and COPD hospitalization: the HUNT Study. 2019. (*Draft of manuscript*)

Abbreviations

AIC	Akaike information criteria
ATS/ERS	American Thoracic Society / European Respiratory Society
AUC	Area under the receiver operating characteristic curve
BOLD	Burden of Obstructive Lung Disease
BMI	Body mass index
C/D	Cumulative dynamic
C-index	Concordance Index
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
ECSC	European Coal and Steel Community
FEV_1	Forced expiratory volume in first second
$FEV_1.Ht^{-2}$	FEV_1 / (Height * Height)
$FEV_1.Ht^{-3}$	FEV_1 / (Height * Height * Height)
FEV_1Q	FEV_1 quotient (FEV_1 / 0.5 for men and FEV_1 / 0.4 for women)
FVC	Forced vital capacity
GEE	Generalized estimation equation
GOLD 2007	GOLD grades
GOLD 2011	ABCD groups
GOLD 2017	New ABCD groups
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GOLD grade 1	Mild severity ($FEV_1/FVC<0.70$ and $ppFEV_1 \geq 80$)
GOLD grade 2	Moderate severity ($FEV_1/FVC<0.70$ and $50 \leq ppFEV_1 < 80$)
GOLD grade 3	Severe severity ($FEV_1/FVC<0.70$ and $30 \leq ppFEV_1 < 50$)
GOLD grade 4	Very severe severity ($FEV_1/FVC<0.70$ and $ppFEV_1 < 30$)
GLI	Global Lung Function Initiative
HR	Hazard ratio
HUNT	Nord-Trøndelag Health Study
HUNT1	Nord-Trøndelag Health Study (1984-1986)
HUNT2	Nord-Trøndelag Health Study (1995-1997)
HUNT3	Nord-Trøndelag Health Study (2006-2008)
HUNT4	Nord-Trøndelag Health Study (2017-2019)
I/D	Incident/dynamic
LLN	Lower limit of normal

LMS	Lambda-mu-sigma
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
Post-BD	Post-bronchodilator
$ppFEV_1$	Percent-predicted forced expiratory volume in first second
ppFVC	Percent-predicted forced vital capacity
Pre-BD	Pre-bronchodilator
PRISm	Preserved ratio impaired spirometry ($FEV_1/FVC \geq 0.70$ and $ppFVC < 80$)
VIF	Variance inflation factor

SUMMARY

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease and ranks as the third leading cause of deaths worldwide. The most frequent respiratory symptoms that people with COPD experience are dyspnoea, chronic cough, chronic sputum production, and wheezing. The changing pattern of aging, air pollution, and smoking warrants the need of continual updated estimates of the prevalence of COPD. COPD has no cure, but proper diagnosis, classification and management can relieve symptoms, improve quality of life, and reduce the risk of hospitalization and death. An international committee, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended post-bronchodilator (BD) spirometry for the diagnosis and classification of COPD but there lacks clear evidence on its prognostic performance compared to other measures such as pre-BD. In 2017, GOLD updated the classification of COPD for the third time, without a strong scientific underpinning for its applicability in guiding therapy and prognosis. Emerging evidence suggests that alternative lung function measures should be considered for the classification of COPD severity, which require further investigation in different populations.

To address the need of future research on the prevalence of COPD and its diagnosis and classification, we used baseline information from the Nord-Trøndelag Health Study (HUNT) and follow-up data on mortality from the Norwegian Cause of Death Registry and COPD hospitalization from the Nord-Trøndelag Health Trust to study 1) the prevalence of COPD in the period 1995-1997 and 2006-2008, 2) the discrimination abilities of pre-BD and post-BD lung function to predict mortality, 3) the discrimination abilities of the GOLD classifications to predict mortality and COPD hospitalization, and 4) the discrimination abilities of a broad range of commonly applied lung function measures to predict mortality and COPD hospitalization.

We found that the overall prevalence of COPD decreased from 1995–1997 to 2006–2008, where it decreased in men but remained relatively stable in women. Mortality was better predicted by post-BD than by pre-BD lung function by a small margin. We observed that the GOLD 2017 classification generally had poor prognostic value in predicting mortality and COPD hospitalization. Our study found that alternative lung function measures such as FEV_1Q that are independent of reference equations were generally more predictive of mortality and COPD hospitalization compared to a broad range of commonly applied lung function measures and classifications.

This thesis provides estimates of the prevalence and change in prevalence of COPD in Nord-Trøndelag improving our knowledge of the disease. It further investigates alternative lung function measures such as FEV_1Q for the classification of COPD severity. Such research may help in prioritizing and planning public health intervention, guiding therapy with improved prognosis and assist in ongoing efforts to prevent COPD.

1. Introduction

1.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a common chronic respiratory disease that is characterized by persistent airflow limitation that is usually progressive [1]. The symptoms of COPD includes dyspnoea, chronic cough, chronic sputum production, and wheezing [1]. COPD is a major cause of chronic morbidity resulting in a substantial global and national socioeconomic burden [2]. Globally, more than 3 million people died of COPD in 2016, which accounted for 5% of all global deaths and 9% of global non-communicable disease deaths [3-5], and it was listed as the third leading cause of death in 2016 [3]. In Norway, chronic diseases in the lower respiratory tract were the third leading cause of death in 2016, where COPD represented a major portion [6]. In Norway, 0.7% of the healthcare budget is due to the burden of COPD [7].

COPD is a progressive and life-threatening respiratory disease that causes breathlessness and predisposes to exacerbation and serious illness [5]. COPD is associated with aging and smoking and both have been established as important risk factors for the development of COPD [1, 5, 8]. Declining trends of smoking and prevalence of COPD has been observed in most western countries [9-11]. However, periodic estimations of the prevalence of COPD and its associated burden are needed to understand the trajectories of COPD and its burden on society to prioritize, plan, and implement public health interventions to reduce its impact on health.

COPD has no cure, but proper diagnosis and treatment could relieve symptoms, improve quality of life, and reduce the risk of hospitalization and death [1, 5]. Until now, substantial research has been conducted for the diagnosis, management, and treatment of COPD [12-14]. However, there is no conclusive evidence that any existing medications for COPD could modify the long-term decline in lung function [1]. In addition, the respiratory medicine community struggles to find the best diagnostic and classification methods for COPD that could improve prediction for outcomes such as hospitalization and mortality. For example, it is unclear whether post-bronchodilator (post-BD) lung function measurements that are used for diagnosis and classification of COPD [1] are better than pre-bronchodilator (pre-BD) in predicting the outcomes [15, 16]. Further research is needed in the area of classification of COPD, so that the future risk of outcomes such as hospitalization and mortality could be reduced or prevented with appropriate management and treatment strategies for people with different levels of COPD severity.

Below is the background to the thesis, which includes an overview of the definition and diagnosis of COPD, airflow limitation, symptoms, exacerbation and hospitalization, mortality, comorbidities, risk factors, prevalence, and classification of COPD.

1.1.1 Definition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998 with a key goal to produce a 'strategic document' for the management of COPD based on the available scientific evidence across the globe [1]. In 2001, the GOLD produced its first report, Global Strategy for Diagnosis, Management and Prevention of COPD. In 2007, 2011, and 2017, major revisions were made to the classification of COPD by GOLD [1]. This strategic document has been received as a reference guideline for the diagnosis, management, and prevention of COPD by many countries including Norway.

The GOLD [1] currently defines COPD as "*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.*"

COPD is a heterogeneous disease both histologically and pathogenically [17, 18]. Conventionally, COPD includes chronic obstructive bronchitis and emphysema with a varying degree of presence, which has differing causes, pathogenic mechanisms, and physiological effects [17, 19]. Chronic airflow limitation is a key characteristic of COPD that is caused by a varying degrees of contribution of chronic obstructive bronchitis and emphysema, which differs from person to person [1, 19].

Conventionally, chronic bronchitis is defined as the presence of cough with phlegm for at least three months for two successive years [1]. Many people with chronic cough and phlegm do not have airflow limitation [17, 18]. However, people with small airways disease such as chronic bronchiolitis might be accompanied by airflow limitation which might be due to inflammation, obstruction, and loss of small airways [1, 19].

Emphysema describes the structural abnormalities in the small airways [19]. Emphysema is a destruction of the gas-exchange surfaces of alveoli [1]. In the presence of emphysema, there are enlargement of air spaces and destruction of lung parenchyma that lead to the loss of lung elasticity [19].

1.1.2 Spirometric definition of COPD and its severity

Spirometry is a non-invasive method that is used for the measurement of dynamic lung volumes. Expiratory flow volume refers to the amount of air a person exhales and can be measured with a spirometer [1]. Vital capacity (VC) is a measure of slow expiration [1]. The forced expiratory flow volume such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) are assessed for defining the airflow limitation [1]. FVC is defined as "*the maximal volume of air*

exhaled with maximally forced effort from a maximal inspiration". FEV_1 is defined as "*the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in litres*" [20].

GOLD defines COPD as a post-BD $FEV_1/FVC<0.70$ and recommends measuring FEV_1 and FVC after the inhalation of bronchodilators [1]. Figure 1 represents the flow volume curves (left) and loops (right) of people with normal lung function and obstructive lung function. The flow volume curves and loops describe that FEV_1 and FVC are reduced in people with COPD, where the reduction in FEV_1 is more compared to FVC.

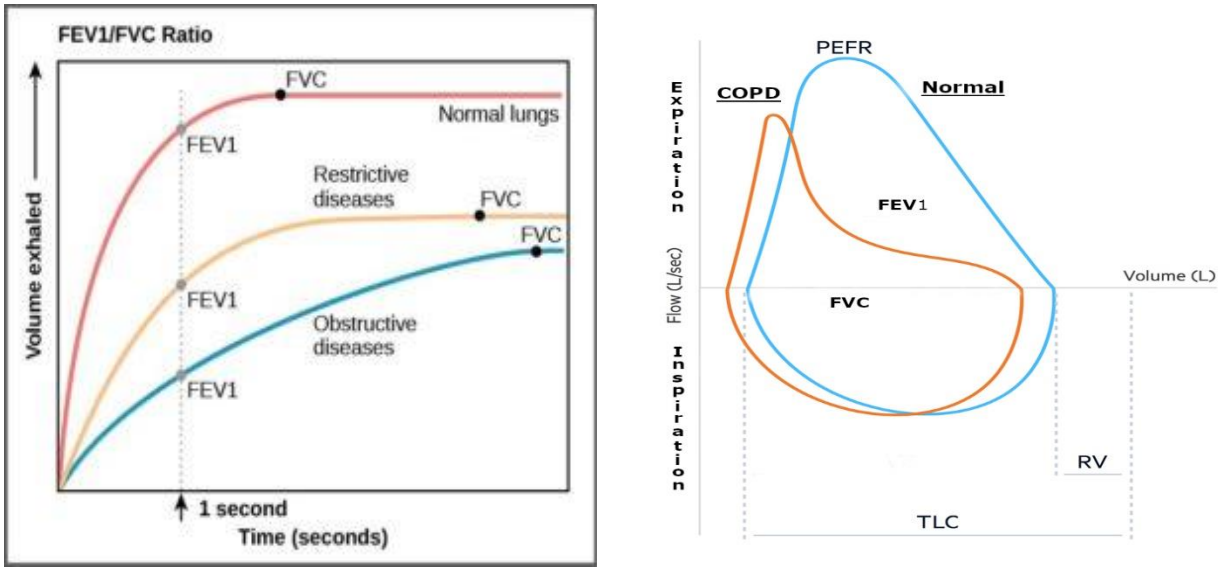


Figure 1. Flow volume curves (left) [21] and loops (right) [22] in people with normal and obstructive lung function.

In 2007, GOLD introduced GOLD grades to classify the severity of airflow limitation [1]. The GOLD grades were based on the predicted values of FEV_1 that are derived using a reference equation derived from a healthy reference population with the same age, sex, height, and ethnicity [23, 24]. The classification of COPD severity based on the $ppFEV_1$ (percent-predicted FEV_1) is presented in Table 1.

Table 1 Classification of severity of COPD according to the GOLD [1].

GOLD grades	**Percent-predicted FEV_1 ($ppFEV_1$)**
Grade 1 (mild severity)	$ppFEV_1 \geq 80$
Grade 2 (moderate severity)	$50 \leq ppFEV_1 < 80$
Grade 3 (severe severity)	$30 \leq ppFEV_1 < 50$
Grade 4 (very severe severity)	$ppFEV_1 < 30$

Abbreviation: COPD (chronic obstructive pulmonary disease), GOLD (global initiative for chronic obstructive lung disease), $ppFEV_1$ (percent-predicted forced expiratory volume in first second)

1.1.3 Airflow limitation

Airflow limitation is a result of structural changes in the lungs due to genetic and environmental factors [1]. The process that results in airflow limitation includes remodelling of the small airways and loss of elastic recoil by parenchymal destruction that result in a progressive decline of FEV_1 and FEV_1/FVC [17].

In COPD, airflow limitation is persistent or irreversible [1]. GOLD and the National Institute for Health and Care Excellence (NICE) recommends the fixed-ratio criteria (FEV_1/ FVC < 0.70) to define COPD [1, 25]. This is the most used approach for defining airflow limitation. However, due to the dynamic nature of lung function, that it changes with a person's age, the use of the fixed-ratio criteria is debated [26]. Normal lung function has three phases; a developmental phase until early adulthood, a plateau for some years, and then a decline phase in later life [27]. Therefore, the fixed-ratio criteria is found to underestimate the prevalence of COPD in the young and overestimate in the elderly [26, 28]. The American Thoracic Society (ATS)/ European Respiratory Society (ERS) in 2005 has recommended the use of lower limit of normal (LLN) criteria for defining airflow limitation and COPD is subsequently defined as FEV_1/ FVC < LLN [23]. LLN is the value of the lower 5^{th} percentile of the frequency distribution of lung function values measured in the reference population [23]. In a normally distributed population, the LLN corresponds to -1.645 standard deviations from the mean. The LLN is based on the reference values from a healthy reference population and takes account of the variability in age, sex, height, and ethnicity of the individuals in the population. Therefore, the use of LLN criteria avoids the issues related to the fixed-ratio criteria that is overestimating the number of COPD cases in elderly populations [23, 26, 28, 29]. However, the reference values largely depend on the reference equation used. Research has suggested many reference equations so far, and while the reference values might have a good fit in a certain population, they do not work for other populations [24, 30-34]. The Global Lung Function Initiative (GLI) Network is an international collaboration that aims to publish lung function reference values for all age groups around the world [35]. In 2012, the GLI published reference values for the ages 3 to 95 years for several ethnic groups [24]. Studies have tested the fit of these reference values in some populations and found that it performed well in most populations [24, 30, 32, 34] but not in some other populations [31, 36]. However, the values have been reported to perform well in Norway based on population-based studies in Hordaland, Tromsø, and the Nord-Trøndelag Health Study (HUNT), the latter being a population based survey from Nord-Trøndelag County in central Norway which this thesis based [24, 30]. Figure 2 describes the variation between the fixed-ratio and the LLN criteria based on the GLI reference equation across the age range [24, 30, 37].

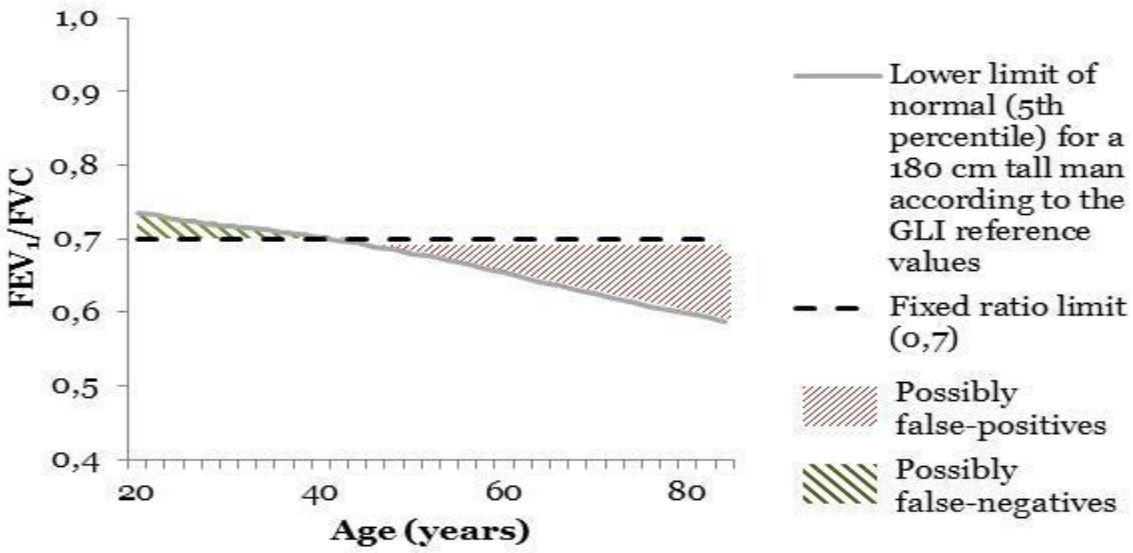


Figure 2. Variation between the fixed-ratio and LLN criteria based on the GLI reference equation [24, 30] across the age range. The figure is adapted from Backman's doctoral thesis with permission [37].

1.1.4 Symptoms

Common respiratory symptoms in people with COPD are dyspnoea, chronic cough, chronic sputum production, and wheezing [1]. The respiratory symptoms have considerable impact on the patients' daily activities and quality of life. Not all people with COPD experience respiratory symptoms or report it [38]. Chronic cough with phlegm is reported by about 30% of people with COPD [39]. Chronic cough with or without phlegm is an early symptom of COPD [40]. People with COPD may also have wheezing but it might not be present in all cases [41]. Dyspnoea is the most characteristic symptom of COPD, which is defined as "*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*" [42]. Respiratory symptoms such as chronic cough with phlegm and dyspnoea are often progressive in nature in people with COPD [1]. The most common causes for the progression of respiratory symptoms are aging, smoking, and undiagnosed COPD [1, 40]. Not all respiratory symptoms are related to COPD. A recent study by Colak et al. [43] observed that the presence of chronic respiratory symptoms in people with normal lung function FEV_1/ FVC ≥0.70 (n=83,889, aged 20-100 years) followed from 2003 through 2018 were associated with respiratory hospitalization and deaths. In the diagnosis and management of COPD, respiratory symptoms play an important role.

1.1.5 Exacerbations and hospitalizations

GOLD defines COPD exacerbations as "*an acute worsening of respiratory symptoms that result in additional therapy*" [1, 44]. COPD exacerbations and hospitalizations are related, however not all

exacerbations lead to hospitalizations. Severe exacerbations often lead to COPD hospitalization [1, 45]. GOLD defines a person with COPD as having a high risk of an exacerbation if having had "at least two exacerbations last year that do not lead to hospitalization or one exacerbation last year that leads to hospitalization" [1, 45]. For the management of COPD and halt the progression of COPD, it is very important to reduce the number of exacerbations [46, 47]. Exacerbations accelerate lung function decline, decrease quality of life, increase mortality, and incur high socio-economic costs [44, 45, 47, 48]. A history of COPD exacerbation is the best predictor of future COPD exacerbations [1, 49]. Lung function decline is associated with exacerbation, where a systematic review of 37 studies by Hoogendoorn et al. [50] estimated (using regression equations) mean frequencies (95% CI) of severe exacerbations (hospitalization) were 0.11 (0.02-0.56) for GOLD grade 1, 0.16 (0.07-0.33) for GOLD grade 2, 0.22 (0.20-0.23) for GOLD grade 3, and 0.28 (0.14-0.63) for GOLD grade 4. Hospitalizations for COPD exacerbations represent the major portion of COPD burden to the health care system [1].

1.1.6 Mortality

COPD is a progressive condition, where its key feature is lung function decline [18, 19, 51]. Decline in lung function has been associated with mortality [13, 15, 16, 52, 53]. A study by Mannino et al. [16] observed that higher $ppFEV_1$ predicted lower risk of mortality. The study observed similar results for pre-BD [hazard ratio (HR) 0.87, 95% CI 0.81-0.94 per 10% increase] and post-BD (HR 0.84, 95% CI 0.77-0.90 per 10% increase) lung function. Vasquez et al. observed that lower levels of $ppFEV_1$ and ppFVC (percent-predicted FVC) even at the age of 21-35 years predicted a higher risk of early cardiopulmonary mortality [53].

1.1.7 Comorbidities

People with COPD often have concomitant chronic illnesses. Common comorbidities are cardiovascular diseases, skeletal muscle dysfunction, diabetes mellitus, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer [45, 48, 54-56]. The coexistence of COPD and comorbidities might have an impact on prognosis [45, 55, 57]. At any level of COPD, comorbidities could develop. Some comorbidities could develop independently of COPD and some are causally related [55]. Shared risk factors such as age, smoking, diet, and inactivity is one of the many reasons for developing comorbidities [45, 54, 57]. GOLD recommends physicians to actively look for comorbidities among people with COPD and to treat each comorbidity specifically [45, 48, 55].

1.1.8 Risk factors

Alterations in normal lung function trajectories through gene-environment interaction is responsible for the development and progression of COPD [27, 45, 55]. Smoking is the most important established factor responsible for the development and progression of COPD [8]. Apart from smoking, exposure to other particles or gases such as organic and inorganic dust, chemical agents and fumes, biomass and coal, and air pollution have been established to increase the risk of developing COPD [45, 48, 58-63].

The best documented genetic factor responsible for the development of COPD is a severe hereditary deficiency of alpha-1 antitrypsin (AATD) [58, 64]. This genetic risk factor accounts for a small portion of COPD risk in the global population [55, 58]. Many other genetic risk factors are assumed to be associated with the development of COPD through their interaction with the environmental factors [58, 65, 66].

Aging is considered as a risk factor of COPD [8]. Studies have observed a higher prevalence of COPD in old age and have found a strong association between increased age and the prevalence of COPD [67-69]. However, it is unclear whether healthy aging is related to COPD or if it reflects the sum of the cumulative exposures throughout life [55]. The prevalence of COPD has historically differed between the sexes in developed countries where men have had a higher prevalence of COPD than women [70, 71]. Recent studies suggest that the gap of prevalence of COPD between men and women is narrowing, which largely reflects the changes in smoking behaviours of men and women [9, 72, 73]. Additionally, studies suggest that women are more biologically susceptible to the effects of smoking than men are [71, 74-76].

Impaired lung growth is considered as one of the important factors for the development of COPD. A study by Lange et al. [51] observed that not only accelerated lung function decline features COPD but low lung function at adulthood is an important feature for the development of COPD [51]. Lung growth is affected by gene-environment interaction occurring during gestation, birth, childhood and adolescence [77, 78]. A meta-analysis confirmed that birthweight is positively associated with FEV_1 in adulthood [79]. Bui et al. [80] observed that childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking were childhood predictors of childhood below average and/or accelerated decline, and persistently low lung function trajectories related to development of COPD [80].

Asthma, airway hyper-responsiveness, chronic bronchitis, and severe childhood respiratory infections have been suggested to increase the risk of COPD [8, 55, 80, 81]. Low socioeconomic status is also associated with an increased risk of COPD [82, 83] but it is unclear which components

of poverty (e.g. exposure to indoor and outdoor pollutants, crowding, poor nutrition, infections, or other factors) are related to the increased risk of COPD [55].

As different risk factors are associated with COPD, the relative distribution of these risk factors in the population might vary the prevalence of COPD.

1.2 Prevalence of COPD and its trend

Prevalence is a measure of disease status or disease burden in the population. The prevalence is the number of people with a disease divided by the total number in a population at a specific point of time [84].

Estimates of the prevalence of COPD may vary for many reasons including differences due to diagnostic criteria, age groups, survey methods, and analytical approaches [69, 85-87]. However, despite these challenges, several studies have aimed to estimate the prevalence of COPD in different populations [69, 85-87]. Several studies have estimated the prevalence of COPD based on self-reported or self-reported doctor diagnosed COPD, which largely underestimates the prevalence of COPD in the population [55, 88, 89]. The majority of studies have used spirometric criteria as a diagnostic method to estimate the prevalence of COPD [10, 69, 90-97]. In 12 Burden of Obstructive Lung Disease (BOLD) centres across the world, the prevalence of COPD according to the fixed-ratio spirometric criteria among people aged ≥40 years ranged from 11.4% (men 15.2%, women 7.8%) to 26.1% (men 26.6%, women 25.7%), where the prevalence of COPD at a BOLD centre (Salzburg) in Austria was highest [69]. The overall prevalence of grade 2 COPD or higher was 10.1% (men 1.8%, women 8.5%) in the 12 BOLD centres [69]. In northern Europe, two studies in northern and central areas of Sweden found the prevalence of COPD to be 8.5% and 16.2%, respectively [10, 91]. A study in Denmark found that the prevalence of COPD was 9.0% (men 11.0%, women 7.0%) [98]. In Iceland, a study found a prevalence of 8.9% (men 8.5%, women 9.3%) [69].

There are few estimates of the prevalence of COPD in Norway. In Western Norway, a prevalence of 14% (men 17%, women 11%) was found in 2003-2005 using the fixed-ratio criteria [97]. Using the same definition of COPD, an international BOLD study found the prevalence of COPD among people 40 years and older to be 18.8% (men 22.6%, women 5.4%) in Bergen in 2006 [69]. In the period 2013-2015, the average number of people with COPD aged ≥40 years diagnosed by regular general practitioner or emergency primary healthcare services were 49,000 each year (men 1.9%, 2.0% women) in Norway [9].

The trends of prevalence of COPD vary between or within a country depending on the population studied [10, 69, 90-97]. In 2016, a meta-analysis estimated that the global prevalence of

COPD in people aged ≥30 years increased from 10.7% in 1990 to 11.7% in 2010 [90]. In the USA, the prevalence of COPD using the fixed-ratio criteria has slightly declined from 14.6% (1988-1994) to 13.5% (2007-2010) [93]. In Nordic countries, the prevalence has remained stable in Finland from 3.3% (1978-1980) to 3.5% (2000-2001) using the LLN criteria but declined in Sweden from 10.5% (1994) to 8.5% (2009) using the fixed-ratio criteria [10, 96]. In Western Norway, an increased prevalence has been observed, from 7% (men 10%, women 4%) in 1996-1997 to 14% (men 17%, women 11%) in 2003-2005 using the fixed-ratio criteria [97].

In general, the prevalence of COPD varies greatly with age, sex and geographic region. Due to differences in prevalence of COPD and trends, estimates of prevalence of COPD from other parts of Norway, and more updated estimates, are warranted.

1.3 Classification of COPD

1.3.1 Pre-BD vs post-BD spirometry in the classification of COPD

Bronchodilators dilate bronchi and bronchioles and thereby reduce airflow limitation [99]. In people with COPD, airflow limitation is variable and primarily irreversible. The use of bronchodilators act upon small reversible components in people with COPD [99]. It is also reported that post-BD lung function reference values differ from pre-BD lung function reference values in the general population [29]. The GOLD recommends post-BD lung function measurements for the diagnosis and classification of COPD [55]. However, post-BD tests are time consuming and not performed as frequently as recommended [100, 101]. Often, only pre-BD lung function is used in clinical practice or in epidemiological studies [16]. The performance of pre-BD and post-BD lung function in predicting mortality has been compared only by a few studies [15, 16, 102]. In a general population (n=5887), Mannino et al. [16] found that the pre-BD and post-BD lung function measurements similarly predicted mortality, where the area under the receiver operating characteristic curve (AUC) for pre-BD and post-BD ppFEV_1 was 69.2% and 69.4%, respectively, during the 15 years of follow-up [16]. However, the approach they used to compare models (i.e. AUC from logistic models) ignores time-to-event information. In contrast to Mannino et al. [16], Chen et al. [15] and Fortis et al. [102] found that post-BD predicted mortality better than pre-BD ppFEV_1. However, Chen et al. [15] included only a limited number of people with COPD (n=300) from a pulmonary department and both Chen et al. [15] and Fortis et al. [102] had limited follow-up of approximately 5 years. Therefore, future research is needed to investigate the prediction ability of pre-BD and post-BD lung function measurements.

1.3.2 GOLD classifications of COPD

The GOLD publish classifications of COPD every year, however major changes to the classification were made in 2007, 2011 and recently in 2017 [55]. In 2007, the GOLD introduced GOLD grades of COPD based on the severity of airflow limitation ($ppFEV_1$) [55]. Due to disease complexity that might not be fully explained by lung function in individual patients; the classification was upgraded in 2011 to include clinical parameters such as the symptom burden and exacerbation history to classify patients into ABCD groups [55, 103]. The ABCD groups are based on the severity of airflow limitation, exacerbation history (number of exacerbations not leading or leading to hospital admission), and symptom burden [modified British Medical Research Council (mMRC) dyspnoea scale or COPD Assessment Test score (CAT)] [55, 57]. The classification of ABCD groups is presented in Figure 3 (left). In Figure 3 (left), the symptom burden is divided into two groups: low symptom (A or C) and high symptom (B or D). The severity of airflow limitation and exacerbation history are used to define low risk (A or B) or high risk (C or D). For example, a person classified as having low risk should have both $ppFEV_1 \geq 50$ and <2 exacerbations (and no exacerbation leading to hospital admission). However, a person is classified as having a high risk if they present with either $ppFEV_1 < 50$ or ≥2 exacerbations (or ≥1 exacerbation leading to hospital admission). In 2017, the GOLD updated the ABCD groups to include only exacerbation history and symptom burden, and used severity of airflow limitation separately [55]. The exclusion of airflow limitation from Figure 3 (right) represents the GOLD 2017 updated ABCD groups.

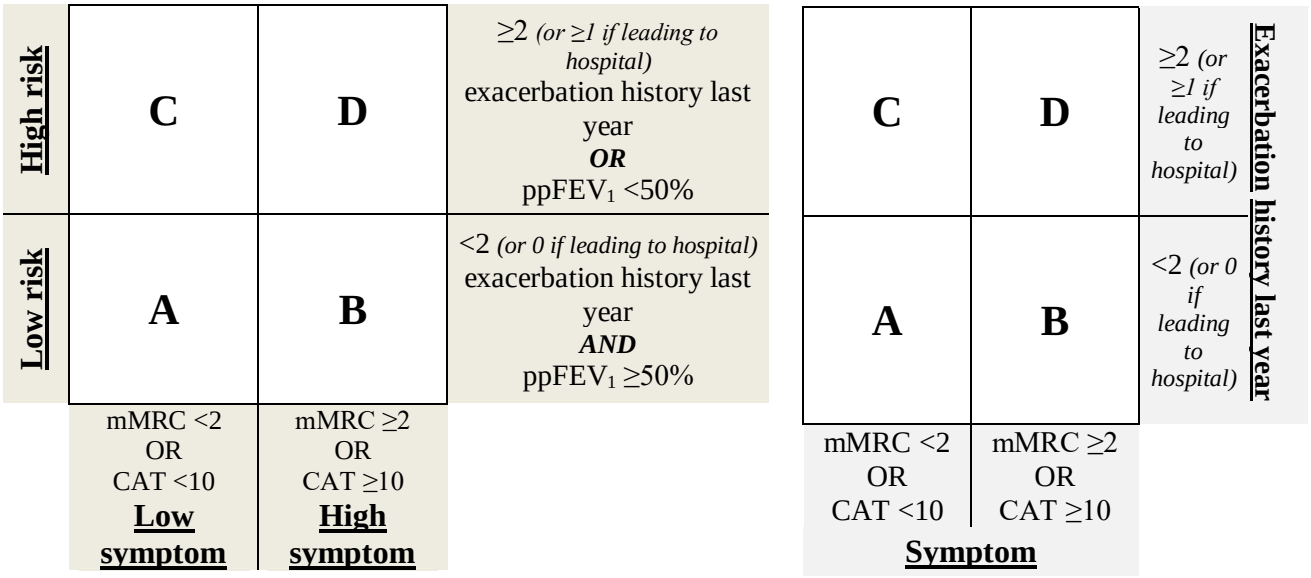


Figure 3. GOLD 2011 (left) and GOLD 2017 (right) classification of COPD [55, 57].

Although the GOLD classifications were meant to guide therapy, clinicians use the classifications for risk classification at an individual level [52]. Therefore, the discrimination abilities of the GOLD 2007 and GOLD 2011 classifications to predict exacerbation and mortality

has been studied [52, 103-106]. Leivseth et al. [106] found that the GOLD 2007 classification predicted mortality better than the GOLD 2011 classification. Johannessen et al. [103] found that the GOLD 2007 and GOLD 2011 classifications predicted respiratory hospitalization similarly well; however, Lange et al. [104] and Chen et al. [105] found that the GOLD 2011 classification was better than the GOLD 2007 in predicting exacerbation. None of these studies used exacerbations as time-to-event data to compare the discrimination abilities. A pooled analysis of 22 cohorts (n=15,632 people with COPD) by Soriano et al. [52] found that GOLD 2007 and GOLD 2011 did not differ significantly in predicting mortality.

Since the publication of the GOLD 2017 classification, the prognostic value of this classification has been debatable with less clear findings [13, 107-109]. To our knowledge, only one study has compared the discrimination abilities of all three GOLD classifications taking mortality as time-to-event data and they found that the GOLD 2017 classification predicted respiratory and all-cause mortality similarly well as the GOLD 2007 and GOLD 2011 classifications [13]. No studies have investigated the risk for COPD hospitalization using the GOLD 2017 classification or compared the discrimination ability with previous GOLD classifications to predict COPD hospitalization. A study by Criner et al. [108] found that the GOLD 2011 and GOLD 2017 classification similarly predicted exacerbation, however, the time-to-event approach was not considered for exacerbations. They found that the GOLD 2011 classification predicted mortality better than the GOLD 2017 classification [108].

In 2019, GOLD published a report suggesting that the GOLD 2017 classification should be considered as a pharmaceutical treatment guide only at the start of diagnosis [110].

Regarding the prediction ability of all GOLD classifications, there were discrepancies in findings between studies on the GOLD classification that are partly explained by methodological differences in statistical approaches and measured outcomes. Hence, further investigation in this regard is warranted.

1.3.3 Spirometric classifications of COPD

The classification of COPD severity is used in guiding therapy and for prognosis [55]. The GOLD recommends GOLD grades [55] and the ATS/ERS recommends ATS/ERS grades [23] based on the post-BD ppFEV_1 lung function measure, which has been widely used in respiratory medicine [55]. ppFEV_1 refers to FEV_1 standardized by the predicted value of FEV_1 in a healthy population. Predicted values are considered to take account of the influence of people's age, sex, height, and ethnicity; however, ppFEV_1 has been criticized due to its susceptibility to physiological variation [111-113]. Studies have shown that ppFEV_1 is a poor predictor of mortality [14, 114]. Accordingly, GOLD grades, which are based on ppFEV_1, poorly predict mortality [14].

An alternative lung function measure, FEV_1 z-score, that depends on a reference equation has been recommend, which refers to the number of standard deviations a measured value of FEV_1 is from the mean of the predicted value of FEV_1 from a reference population [24, 115]. As $ppFEV_1$, FEV_1 z-score takes account of the influence of people's age, sex, height, and ethnicity; however, the FEV_1 z-score are not considered to be influenced by issues related to the variation in age [111, 112, 116]. Vaz Fragoso et al. [111] used the reference equation from National Health and Nutrition Examination Survey (NHANES) III [117] and found that severe COPD based on FEV_1 z-score was associated with high risk of death and respiratory symptoms. Tejero et al. [115] found that FEV_1 z-score was a poorer predictor of mortality than $ppFEV_1$ where they calculated lung function measures using the GLI reference equation [24]. These studies may demonstrate that the performance of the classification of COPD severity based on $ppFEV_1$ and FEV_1 z-score to predict outcomes such as mortality and exacerbation/COPD hospitalization could vary with the reference values because they depend on the choice of reference equations [24, 30, 34, 118]. Furthermore, studies have observed that the GLI reference equation better describes the healthy population than the European Coal and Steel Community (ECSC) reference equation [24, 30, 119].

Studies have recommended other lung function measures such as FEV_1 standardized by squared height ($FEV_1.Ht^{-2}$) [14, 120] and cubic height ($FEV_1.Ht^{-3}$), which account for size and indirectly some sex differences [121-123]. Additionally, Miller et al. [121] recommended the FEV_1 quotient (FEV_1Q), where FEV_1Q is a sex-specific lowest first percentile of FEV_1 distribution that takes account of sex and some size differences in lung function [121].

Studies by Miller et al. [14, 121, 124] found that lung function measures such as $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q, which are independent of reference equations, correlate better with mortality than those that depend on reference equations, where they used ECSC reference equation for the calculation of predicted values. Several studies have also investigated these lung function measures and their respective classifications of COPD severity [113-115, 123, 125, 126]. Only Huang et al. [113] and Hegendorfer et al. [125] have compared the lung function measures mentioned above to predict mortality and exacerbation [113] or all-cause hospitalizations [125]. They found that FEV_1Q performed better than other lung function measures. However, Huang et al. [113] included only a small number of people with COPD (n=296) and Hegendorfer et al. [125] included 501 people with only 14% of people with asthma/COPD. No study has compared the discrimination abilities of lung function measures for COPD hospitalization. Therefore, further investigation is needed to compare the predictive abilities of a range of lung function measures and their respective methods of classification of COPD severity.

2. Aims

The overall aim of this thesis is to investigate the prevalence of COPD and to compare the abilities of different methods of classification of COPD to predict all-cause mortality and COPD hospitalization.

The individual study aims were:

1) To estimate the prevalence and change in prevalence of pre-BD spirometry COPD in the period 1995-1997 and 2006-2008 using fixed-ratio and LLN criteria. [Paper I]
2) To compare the discrimination abilities of pre-BD and post-BD lung function to predict all-cause mortality in people with airflow limitation or COPD over 20 years' follow-up. [Paper II]
3) To compare the discrimination abilities of the GOLD 2007, GOLD 2011, and GOLD 2017 classifications to predict all-cause mortality and COPD hospitalization over 20 years' follow-up. [Paper III]
4) To compare the discrimination abilities of ppFEV_1, FEV_1 z-score, $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q lung function measures and their respective methods of classification of COPD severity to predict all-cause mortality and COPD hospitalization over 20 years' follow-up. [Paper IV]

3. Materials and methods

3.1 Study design

A cross-sectional design was used to address the 1st aim [Paper I] (Figure 4). This design is a type of observation study, where information on an exposure and/or outcome are collected at a specific point of time from a population or representative sample [127]. Commonly, the cross-sectional design is used to estimate the prevalence of disease.

A cohort design was used to estimate the incidence of COPD in Paper I and for the other three aims of this thesis [Paper II, III, and IV] (Figure 4). In a cohort design, the information on the exposure is collected from a group of people free from the outcome (such as disease) at a point in time (baseline) and they are followed for a certain time to observe the development of the outcome of interest (incidence) at another point in time (follow-up) [127]. Commonly, cohort designs are used to study incidence of disease.

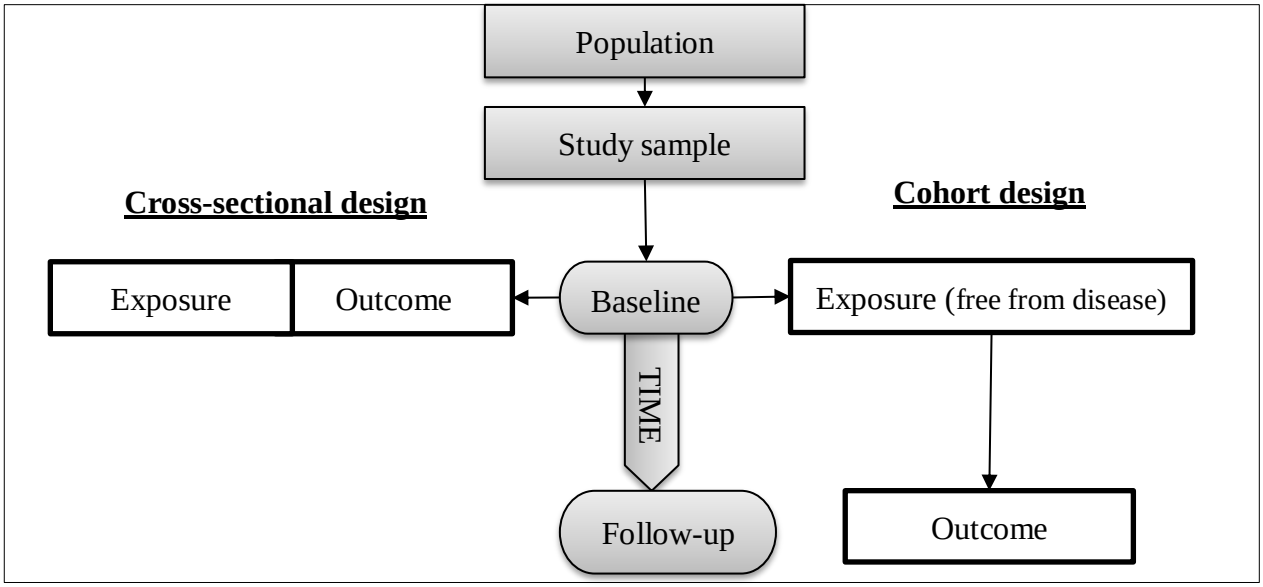


Figure 4. Study design

3.2 Study population and data collection

This thesis is based on data from the HUNT, the Norwegian Cause of Death Registry, and The Nord-Trøndelag Hospital Trust. Due to the unique personal identification number of all inhabitants of Norway, data from different sources were linked. Further detail on each of these data sources is described below.

3.2.1 HUNT

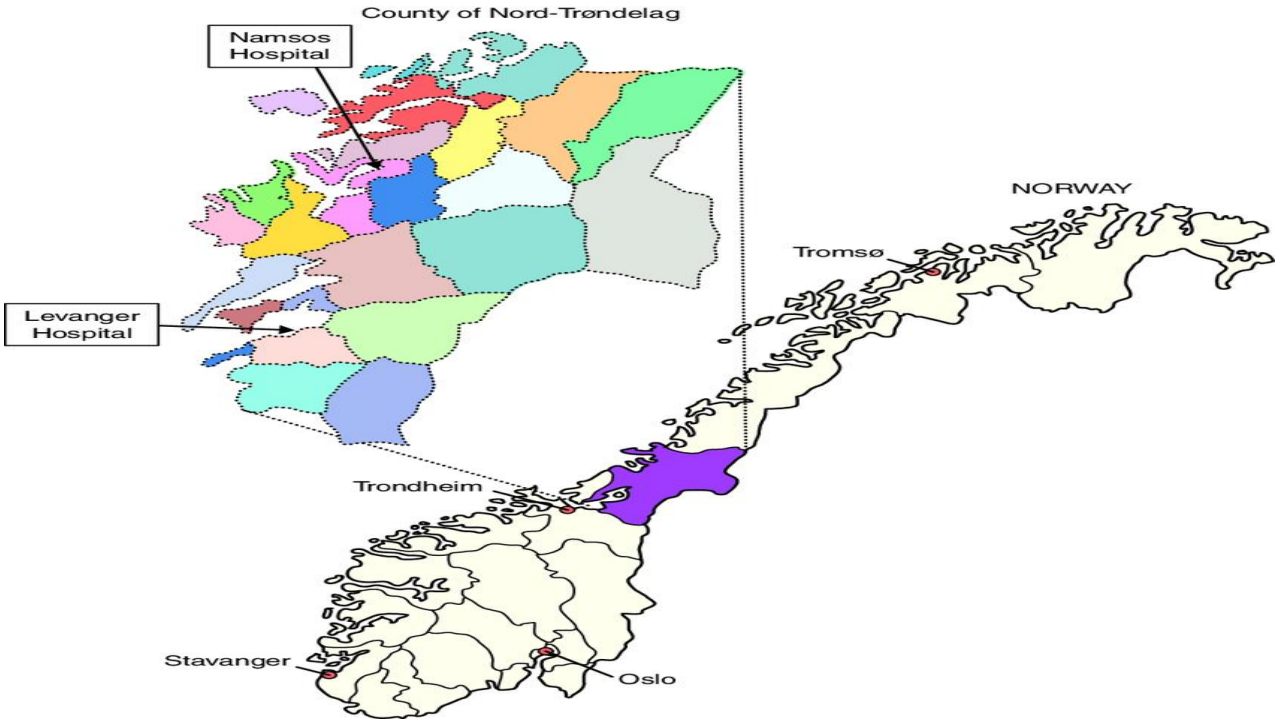


Figure 5. Norway and Nord-Trøndelag County [128]

Until 2018, Nord-Trøndelag was a county in central Norway (Figure 5). It was later merged with the county of Sør-Trøndelag to form a new county, Trøndelag. Nord-Trøndelag had a homogenous and stable population, and in many respects it can be considered representative of Norway. In 1995, the population of Nord-Trøndelag was 127,000, with 97% being Caucasians [129].

The HUNT is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Nord-Trøndelag County Council (now part of Trøndelag) and the Norwegian Institute of Public Health.

The HUNT is a comprehensive health survey that invited the entire adult population (20 years or older) of former Nord-Trøndelag to attend a clinical examination and answer questionnaires [130]. The HUNT was conducted in the periods 1984–1986 (HUNT1), 1995–1997 (HUNT2), 2006–2008 (HUNT3), and recently in 2017-2019 (HUNT4, data not available until October 2019) [129, 130]. The adolescent population (13-19 years old) of Nord-Trøndelag was also invited in the periods 1995-1997 (Young-HUNT1), 2000-2001 (Young-HUNT2), and 2006-2008 (Young-HUNT3) [131]. The HUNT includes many sub-studies such as the Lung Study, the Diabetes Study, osteoporosis studies and chronic pain studies, where selected participants from the HUNT were invited to undergo further examinations, interviews and to fill out questionnaires for specific diseases or health outcomes [130].

The HUNT collected a wide range of information on self-reported illness, diseases, life-style and health related factors, and socio-economic position through self-reported questionnaires. It recorded information on factors such as age, sex, place of residence, smoking, smoking pack-years (estimated by reported smoking exposure), education, physical activity, diabetes, asthma, cardiovascular disease, wheezing/dyspnoea, chronic bronchitis, cough phlegm, cough daily, and COPD. All participants underwent a clinical examination including measurements such as height, weight, waist and hip circumference, and blood pressure. Blood samples were taken to collect information on cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and glucose concentrations [129, 130]. In addition to the information collected in the HUNT, the HUNT Lung Study collected information on lung health through questionnaire, interview, and flow volume spirometry at pre-BD and post-BD stations [118].

This thesis analysed the data from the HUNT2 and the HUNT3 Lung Study as the HUNT1 did not include information on spirometry, and the HUNT4 data were not available.

HUNT2

Among 93,898 invited, 65,237 (69.5%) participated in the HUNT2. Among the HUNT2 participants, a 5% random sample and symptom sample were invited to attend the HUNT2 Lung Study. The symptom sample included participants who reported at least either having/ever had asthma or having/ever had asthma medication or ever had attacks of wheezing/breathlessness during the last 12 months. All the participants in the HUNT2 Lung Study performed pre-BD spirometry. For post-BD spirometry, participants having an airflow limitation (pre-BD $FEV_1/FVC < 0.75$ or $FEV_1 < 80\%$ of predicted using the ECSC equations [132]) from 5 urban municipalities and all participants from 19 rural municipalities were invited. We used less stringent airflow limitation criteria to allow for future changes to the GOLD guidelines definition of COPD. Participants performed post-BD spirometry 30 minutes after inhalation of 1 mg terbutaline. Further details of spirometry measurements are described below.

HUNT3

Among 93,860 invited, 50,807 (54.1%) participated in the HUNT3. Among the HUNT3 participants, a 10% random sample and symptom sample were invited to attend the HUNT3 Lung Study. The symptom sample included participants reporting symptoms as per the symptom sample in the HUNT2 Lung Study in addition to having/ever had chronic bronchitis/emphysema/COPD or having/ever had respiratory problems (coughing, short of breath or wheezing) due to work. All the

participants in the HUNT3 Lung Study were invited for pre-BD spirometry. Post-BD spirometry was not performed during the HUNT3 Lung Study.

3.2.2 Spirometry

During the HUNT Lung Study, participants reported on respiratory health and performed flow volume spirometry. Spirometry was performed before (pre-BD) and after (post-BD) 30 minutes from inhalation of 1 mg terbutaline [30, 133]. Using spirometry, the measurements of expiratory flow volume such as FEV_1 and FVC were recorded.

Heated pneumotachograph spirometers were used in the HUNT2 and the HUNT3 [30]. The spirometers were easy to hold, reliable, reproducible, and easy to clean [134]. However, the spirometers drifted with temperature, needed regular calibration if moved, were affected by condensation, and accuracy error calibration procedures needed to be performed regularly. Therefore, regular checks for holes in the sensor, channel plugging and excess moisture were performed. Calibration was performed each morning and afternoon with a one or three litre syringe. In addition, technicians checked their own lung function every day at each workstation. The room temperature ranged from 19 to 24 ^{o}C [30, 134].

During spirometry, all participants were seated, wore nose clips and received standardized instruction from trained technicians [30].

FEV_1 and FVC were measured in accordance with the 1994 ATS-criteria in the HUNT2 [133] and the 2005 ATS/ERS criteria in the HUNT3 [20]. Quality control methods applied for acceptability and reproducibility of spirometry were similar in the HUNT2 and the HUNT3, and the same 2-3 trained persons performed all evaluations.

The acceptability criteria for the blows were [30, 134]:

(1) The maximal effort curve and the back-extrapolated volume should be less than 5% of FVC or 150 ml.

(2) During the two last seconds of expiration, the volume change should not exceed 40 ml.

(3) Minimum FVC exhalation time of 6 second was not strictly applied.

The reproducibility criterion was [30, 134]:

(1) The two largest FEV_1 and FVC curves should differ by less than 200 ml.

At least three spirometric manoeuvres were performed and the curves were graded A-F partly in line with the methods described by Hankinson et al. [30, 135]. All the curves graded A-C were accepted and included in the thesis [30]. The summary of the quality control methods is described in Table 2.

Table 2. Quality control methods for acceptability and reproducibility of spirometry in the HUNT2 and the HUNT3.

Grade	Acceptable blows (n)	Repeatable	EOT criteria for FVC with exhalation >6 seconds
A	≥ 3	< 150 ml	NA
B	2	< 150 ml	NA
C	≥ 2	< 200 ml	NA
D	≥ 2	< 250 ml	NA
F	1	NA	NA

HUNT (Nord-Trøndelag Health Study), EOT (End of Test Criteria), NA (Not applicable), FVC (forced vital capacity), ml (millilitres)

3.3 Study samples

3.3.1 Paper I

Paper I included adults aged ≥40 years. Among adults aged ≥40 years, 44,384 participated in the HUNT2 (75.2% participation) and 39,331 participated in the HUNT3 (61.6% participation).

Approximately 21% (n=9423) of participants in the HUNT2 were invited to the HUNT2 Lung Study, which included a 5% random sample (n=2300) and a symptom sample (n=7123). In the HUNT2 Lung Study, 79.7% (n=7512) participated in pre-BD spirometry where 4.7% (n=354) having unacceptable spirometry were excluded. Participants with acceptable pre-BD spirometry were 7158 (Figure 6).

Approximately 34% (n=13,258) of the participants in the HUNT3 were invited to the HUNT3 Lung Study, which included a 10% random sample (n=4008) and a symptom sample (n=9250). In the HUNT3 Lung Study, 66.9% (n=8875) participated in spirometry and 1.0% (n=85) having unacceptable spirometry and 2 participants having no information on predicted probability of response weight were excluded. From the HUNT3, 8788 participants were included in this study (Figure 7).

3.3.2 Paper II

Among adults aged ≥40 years, 44,384 participated in the HUNT2 (75.2% participation). A 5% random sample (n=2300) and symptom sample (n=7123) were invited to perform spirometry in the HUNT2 Lung Study [129, 130]. 79.7% (n=7512) participated in pre-BD spirometry where 4.7% (n=354) having unacceptable spirometry were excluded. Participants with acceptable pre-BD spirometry were 7158 (Figure 8).

At the post-BD screening stations, participants having an airflow limitation (pre-BD FEV_1/FVC <0.75 or FEV_1<80% of predicted using the ECSC equations [132]) from the 5 urban municipalities and all participants from the 19 rural municipalities were invited to attend post-BD spirometry screening stations. Among them, 4178 participated (73.6% of invitees) and 3840 had acceptable post-BD spirometry manoeuvres excluding 338 (8.1%) with unacceptable spirometry.

Paper II included participants performing both pre-BD and post-BD spirometry (n=3723). Participants with acceptable pre-BD and post-BD lung function and having airflow limitation (pre-BD FEV_1/FVC <0.75 or FEV_1<80% of predicted using the ECSC equations [132]) were included in the analysis (n=2538) because we required all the analyses to have the same number of participants when using pre-BD or post-BD lung function. Additionally, participants with acceptable pre-BD and post-BD lung function and having COPD were included in the analysis (n=1262) (Figure 8). COPD was defined as participants having persistent airflow limitation (pre-BD and post-BD FEV_1/FVC<0.70) and [respiratory symptoms (daily cough in periods, cough with phlegm, wheezing, or dyspnoea) and/or self-reported doctor-diagnosed COPD] [55].

3.3.3 Paper III

Paper III included participants with acceptable post-BD spirometry (n=3840) from the HUNT2. After exclusion of 50 participants with missing information on dyspnoea and/or exacerbation, we included 1300 participants with acceptable post-BD spirometry and COPD in the analysis (Figure 8). COPD was defined as post-BD FEV_1/FVC<0.70 and [respiratory symptoms (daily cough in periods, cough with phlegm, wheezing, or dyspnoea) and/or self-reported doctor-diagnosed COPD] [55].

3.3.4 Paper IV

There were 1350 people with COPD in the HUNT2. COPD was defined as participants having post-BD FEV_1/FVC<0.70 and [respiratory symptoms (daily cough in periods, cough with phlegm, wheezing, or dyspnoea) and/or self-reported doctor-diagnosed COPD] [55]. When COPD was additionally defined as post-BD FEV_1/FVC z-scores< -1.645, there were 894 people with COPD [24, 30].

For the analysis in Paper IV, we included 890 people with COPD who satisfied both the fixed-ratio and the LLN criteria because we required all the analyses to have the same number of participants when using each of the COPD classifications (Figure 8) [24, 55].

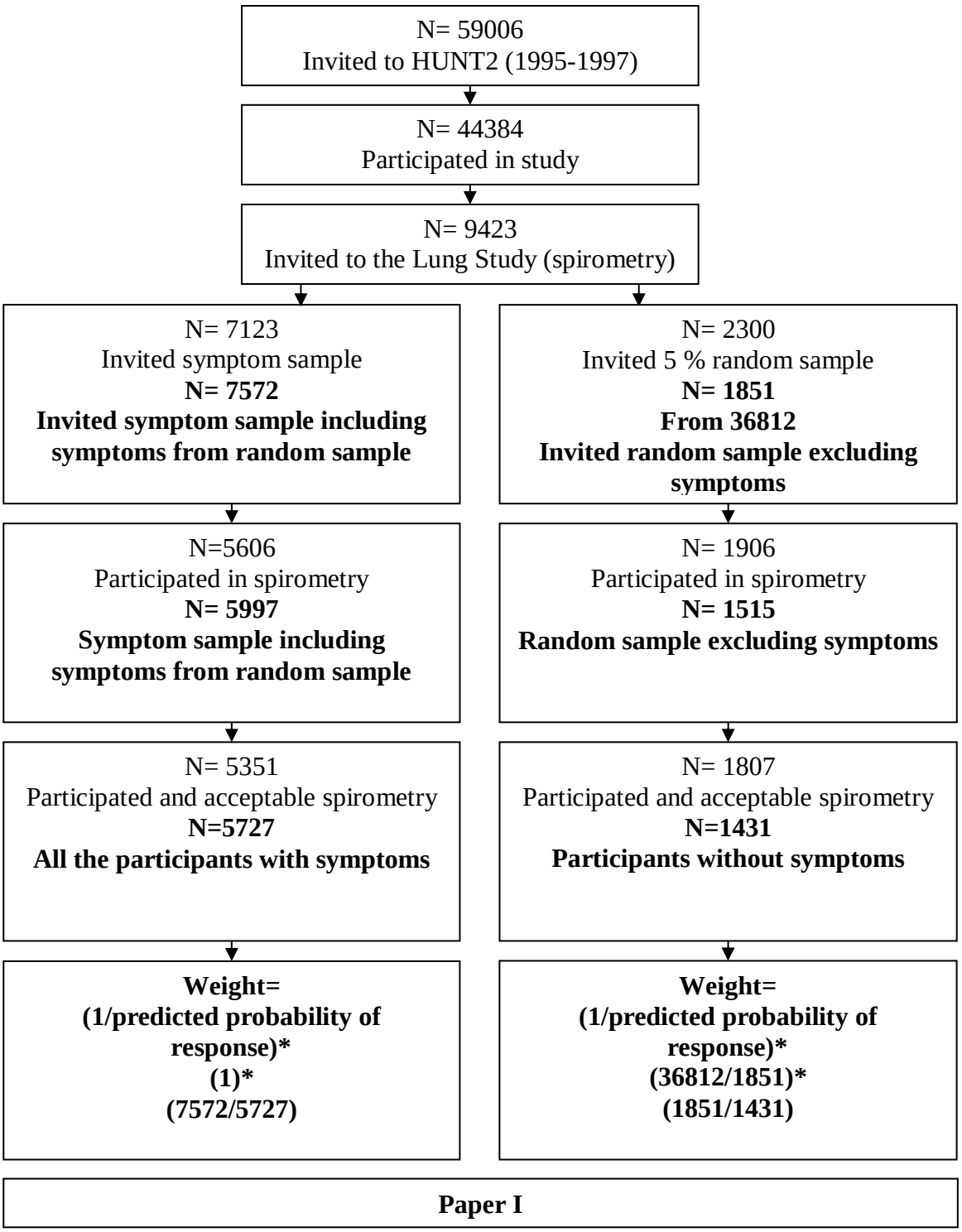


Figure 6. Flow chart of the HUNT2 among adults aged ≥40 years [Paper I].

Abbreviations: HUNT (Nord-Trøndelag Health Study).

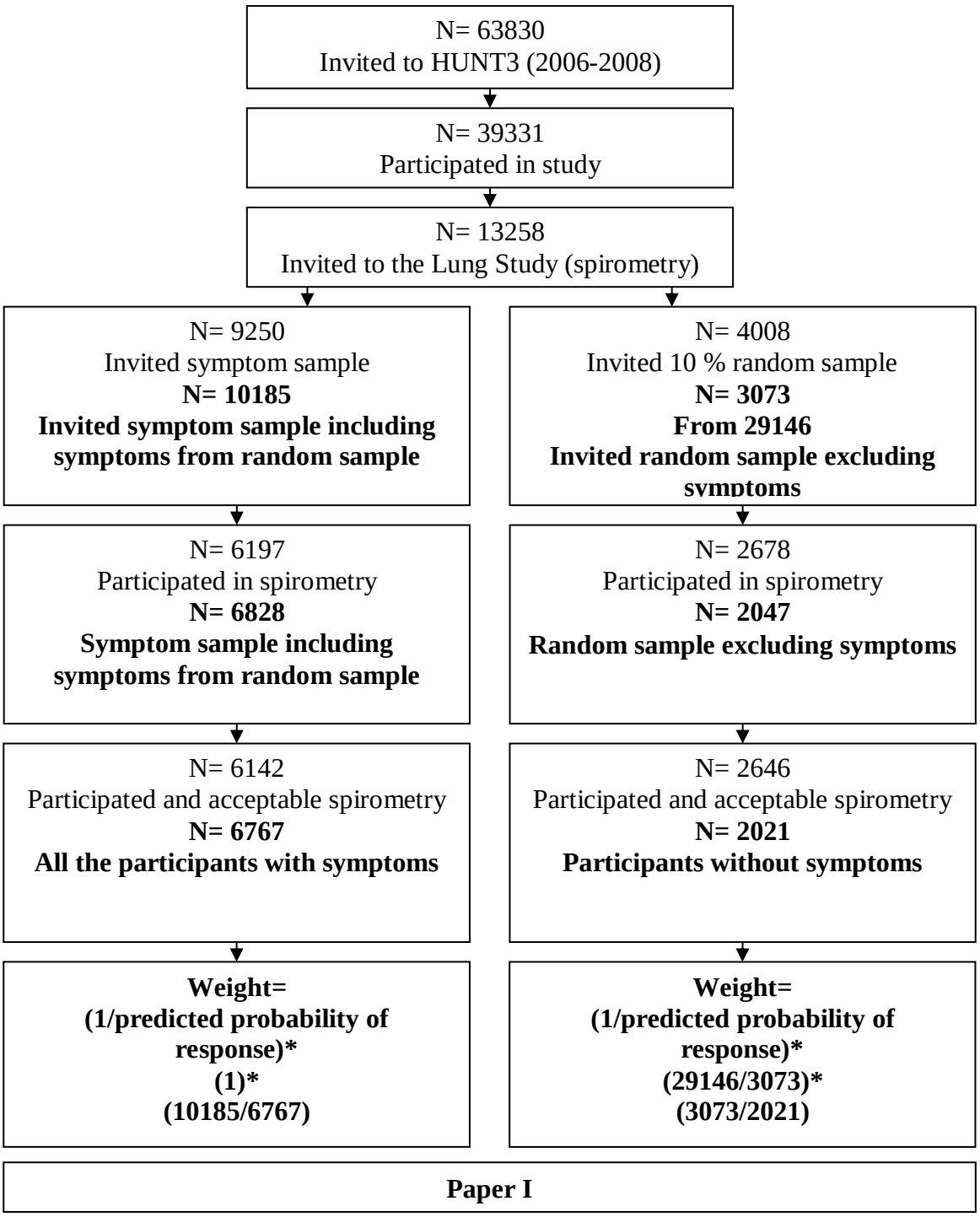


Figure 7. Flow chart of the HUNT3 among adults aged ≥40 years [Paper I].

Abbreviations: HUNT (Nord-Trøndelag Health Study).

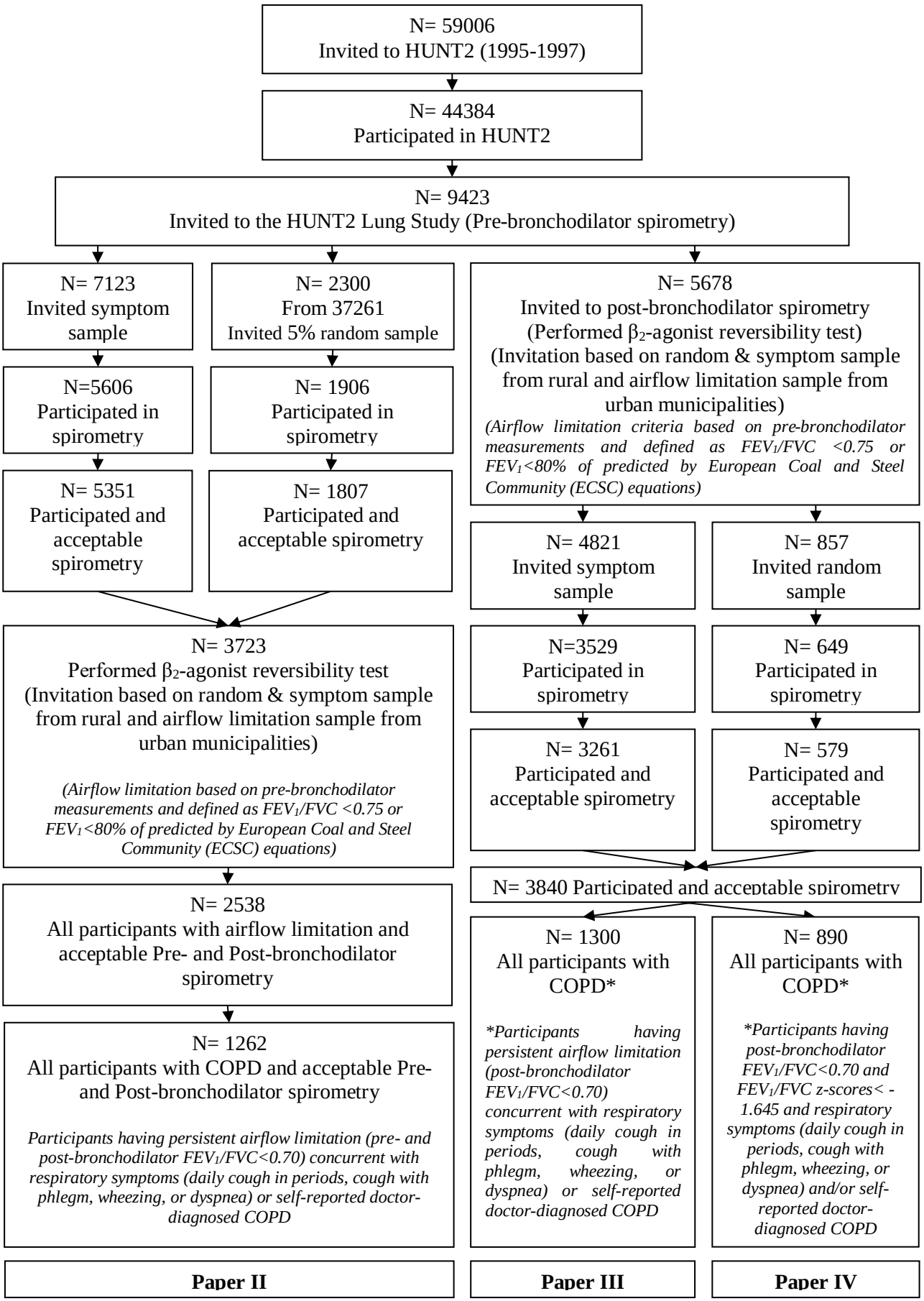


Figure 8. Flow chart of the HUNT2 among adults aged ≥40 years [Paper II, III, and IV]

Abbreviations: HUNT (Nord-Trøndelag Health Study).

3.4 Study variables

3.4.1 Lung function measures

The lung function measures used in this thesis are described below.

percent-predicted FEV_1

FEV_1 and FVC were standardized by the respective predicted values to calculate $ppFEV_1$ and ppFVC, respectively. The GLI-2012 reference equation was used to calculate the predicted values of FEV_1 and FVC based on lambda-mu-sigma (LMS) methods using the Generalized Additive Model for Location, Scale and Shape (GAMLSS) package [24, 30]. In the LMS method, the median (Mu) represents how FEV_1 changes with age, sex, height, and ethnicity; the coefficient of variation (Sigma) models the spread of reference values; and the skewness (Lambda) models departure from normality [24, 136]. The GLI reference values were found to be the best fit with the Norwegian population [30].

The GLI reference equation was [24]:

$Y = a + b \cdot H + c \cdot A + \text{age-spline} + d1 \cdot \text{group} + d2 \cdot \text{group} \cdot A$

Where Y = dependent variable, H = standing height (cm); A = age (year); a, b, c, d1 and d2 are coefficients which vary for each ethnic group, and spline is an age-specific contribution from the spline function. Group is a dummy variable with values 0 or 1 indicating ethnicity, where Caucasians are the reference.

FEV_1 z-score

The GLI-2012 reference equation was used to derive FEV_1 z-scores and FVC z-scores based on LMS methods using the GAMLSS package [24, 30]. Z-scores represent the standard normal distribution of lung function measures that takes account of the variability in age, sex, height, and ethnicity of the individuals in the population [24, 112].

$FEV_1.Ht^{-2}$

FEV_1 was standardized by squared height to calculate the $FEV_1.Ht^{-2}$ [14].

The general form of the equation was FEV_1 / (Height * Height).

FEV_1 was measured in litres and height was measured in meters. The unit of $FEV_1.Ht^{-2}$ was L/m^2.

$FEV_1.Ht^{-3}$

FEV_1 was standardized by cubed height to calculate the $FEV_1.Ht^{-3}$ [121].

The general form of the equation was FEV_1 / (Height * Height * Height).
FEV_1 was measured in litres and height was measured in meters. The unit of $FEV_1.Ht^{-3}$ was L/m^3.

FEV_1Q

FEV_1 was standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of the FEV_1 distribution to calculate the FEV_1 quotient (FEV_1Q) [121].

The general form of the equation was FEV_1 / 0.5 for men and FEV_1 / 0.4 for women.
FEV_1 was measured in litres.

3.4.2 COPD

Self-reported doctor diagnosed COPD

In the HUNT2 Lung Study, participants were asked, "*Have you been diagnosed as having chronic bronchitis or emphysema by a doctor?"* through questionnaire. In the HUNT3 Lung Study, participants were asked, "*Have you ever been diagnosed as having chronic bronchitis, emphysema, or COPD by a doctor?"* during an interview. The clinical diagnosis of COPD was based on airflow limitation and respiratory symptoms.

LLN criteria

The ATS/ERS has recommended LLN criteria to define COPD [23]. In Paper I, we used the GLI equation for the LLN criterion, FEV_1/FVC z-score< -1.645 [24]. LLN represents the lowest 5^{th} percentile of a normally distributed lung function measures in a population, where the value of -1.645 corresponds to LLN [23, 24].

Fixed-ratio criteria

Until 2016, GOLD defined COPD as persistent airflow limitation [55]. In Paper I, we used this definition for the calculation of prevalence and incidence of COPD ($FEV_1/FVC<0.70$) using pre-BD measurements.

From 2017, GOLD defined COPD as persistent airflow limitation concurrent with respiratory symptoms [55]. In Papers II, III, and IV, we used this definition so that the results could have the most direct clinical usefulness.

In Paper II, we defined COPD as having persistent airflow limitation (pre-BD and post-BD $FEV_1/FVC<0.70$) and [respiratory symptoms and/or self-reported doctor-diagnosed COPD] [55]. Respiratory symptoms included daily cough in periods, cough with phlegm, wheezing, or dyspnoea.

In Paper III, we defined COPD as having persistent airflow limitation (post-BD $FEV_1/FVC<0.70$) and [respiratory symptoms and/or self-reported doctor-diagnosed COPD] [55]. Respiratory symptoms were as above.

In Paper IV, we defined COPD as having persistent airflow limitation (post-BD $FEV_1/FVC<0.70$ and FEV_1/FVC z-score< -1.645) and [respiratory symptoms and/or self-reported doctor-diagnosed COPD] [55]. Respiratory symptoms were as above.

Modified-GOLD categories

In Paper II, lung function measurements were classified into modified-GOLD categories as follows: normal ($FEV_1/FVC \geq 0.70$ & $ppFVC \geq 80$), preserved ratio impaired spirometry (PRISm [137]) ($FEV_1/FVC \geq 0.70$ & $ppFVC<80$), mild obstruction ($FEV_1/FVC<0.70$ & $ppFEV_1 \geq 80$), moderate obstruction ($FEV_1/FVC<0.70$ & $80>ppFEV_1 \geq 50$), severe obstruction ($FEV_1/FVC<0.70$ & $50>ppFEV_1 \geq 30$), and very severe obstruction ($FEV_1/FVC<0.70$ & $ppFEV_1<30$) [55, 137].

3.4.3 GOLD classifications of COPD

The GOLD 2007 classification (GOLD grades)

The GOLD 2007 classification (GOLD grades) [55] was based on the severity of airflow limitation and described in Table 1.

The GOLD 2011 classification (GOLD groups) (ABCD groups)

The GOLD 2011 classification (ABCD groups) [55, 57] was based on severity of airflow limitation, exacerbation history, and symptom burden and described in Figure 3 (left). Symptom burden was based on our local dyspnoea scale where "dyspnoea when walking" ("Do you become short of breath when walking on flat ground at a normal pace?") corresponds to the 2nd scale on the mMRC dyspnoea scale. All the questions on our local dyspnoea scale were similar to those of the mMRC dyspnoea scale but were phrased as individual "yes or no questions" [138-140]. Exacerbation history was based on two questions: "Have you ever taken cortisone tablets for breathing problems/asthma?" and "Have you previously taken it in periods when your illness had worsened?" Participants answering 'yes' to both questions and having ≥2 cortisone courses during the last year or ≥3 courses during the last two years were categorized as having a high exacerbation risk.

The GOLD 2017 classification (new ABCD groups)

The GOLD 2017 classification was only based on symptom burden and exacerbation history [55] and described in Figure 3 (right). We used the questions on symptom burden and exacerbation history as described above for the GOLD 2011 classification.

3.4.4 Other methods of classification of COPD

Based on ppFEV$_1$, GOLD has recommended *GOLD grades* [55] and ATS/ERS has recommended *ATS/ERS grades* [23] for the classification of COPD severity. Based on FEV$_1$ z-score, Quanjer et. al. recommended *FEV$_1$ z-score grades* [112] for the classification of COPD severity. Based on FEV$_1$.Ht^{-2} [14, 120], FEV$_1$.Ht^{-3} [121-123], and FEV$_1$Q [121], no widely acceptable cut-points for the classification of COPD severity have been recommended. Following other studies [113, 114, 121], we therefore used *quartiles* of *FEV$_1$.Ht^{-2}*, *FEV$_1$.Ht^{-3}*, and *FEV$_1$Q* distribution on our study population for the classification of COPD severity. To have comparable estimates with these quartiles, we have also generated the *quartiles* of *ppFEV$_1$* and *FEV$_1$ z-score*.

The different lung function measures and their respective methods of classification of COPD severity used in this thesis are presented in Table 3.

Table 3. Different lung function measures and their respective methods of classification of COPD severity.

Lung function measures							
ppFEV$_1$ [¶]			FEV$_1$ z-score [§]		FEV$_1$.Ht^{-2} [ǂ]	FEV$_1$.Ht^{-3} [¥]	FEV$_1$Q [†]
Classification of COPD severity							
ppFEV$_1$ quartiles	GOLD grades	ATS/ERS grades	FEV$_1$ z-score quartiles	FEV$_1$ z-score grades	FEV$_1$.Ht^{-2} quartiles	FEV$_1$.Ht^{-3} quartiles	FEV$_1$Q quartiles
quartile 1 (ppFEV$_1$≥76)	grade 1 (ppFEV$_1$≥80)	grade 1 (ppFEV$_1$≥70)	quartile 1 (FEV$_1$ z-score≥ -1.6)	grade 1 (FEV$_1$ z-score≥ -2.0)	quartile 1 (FEV$_1$.Ht^{-2}≥0.79)	quartile 1 (FEV$_1$.Ht^{-3}≥0.46)	quartile 1 (FEV$_1$Q≥5.0)
quartile 2 (76>ppFEV$_1$≥65)	grade 2 (80>ppFEV$_1$≥50)	grade 2 (70>ppFEV$_1$≥50)	quartile 2 (-1.6>FEV$_1$ z-score≥ -2.2)	grade 2 (-2.0>FEV$_1$ z-score≥ -3.0)	quartile 2 (0.79>FEV$_1$.Ht^{-2}≥0.64)	quartile 2 (0.46>FEV$_1$.Ht^{-3}≥0.38)	quartile 2 (5.0>FEV$_1$Q≥4.0)
quartile 3 (65>ppFEV$_1$≥53)	grade 3 (50>ppFEV$_1$≥30)	grade 3 (50>ppFEV$_1$≥35)	quartile 3 (-2.2>FEV$_1$ z-score≥ -2.8)	grade 3 (-3.0>FEV$_1$ z-score≥ -4.0)	quartile 3 (0.64>FEV$_1$.Ht^{-2}≥0.50)	quartile 3 (0.38>FEV$_1$.Ht^{-3}≥0.30)	quartile 3 (4.0>FEV$_1$Q≥3.0)
quartile 4 (ppFEV$_1$<53)	grade 4 (ppFEV$_1$<30)	grade 4 (ppFEV$_1$<35)	quartile 4 (FEV$_1$ z-score< -2.8)	grade 4 (FEV$_1$ z-score< -4.0)	quartile 4 (FEV$_1$.Ht^{-2}<0.50)	quartile 4 (FEV$_1$.Ht^{-3}<0.30)	quartile 4 (FEV$_1$Q<3.0)

[¶] - percent-predicted forced expiratory volume in first second (ppFEV$_1$) based in GLI-2012 equation.
[§] - forced expiratory volume in first second (FEV$_1$) z-score based on GLI-2012 equation.
[ǂ] - FEV$_1$ standardized by squared meter of height.
[¥] - FEV$_1$ standardized by cubic meter of height.
[†] - FEV$_1$ standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV$_1$ distribution.

Table 4. Questions on respiratory symptoms and asthma.

Characteristics	**Question**	**Source**
Asthma ever	Do you have or have you had asthma?	HUNT- main questionnaire
Doctor-diagnosed COPD	Have you been diagnosed as having chronic bronchitis or emphysema by a doctor?	HUNT2 Lung Study – main questionnaire
	Have you been diagnosed as having chronic bronchitis, emphysema, or COPD by a doctor?	HUNT3 Lung Study – interview
Wheezing/dyspnoea	Have had any kind of attack of wheezing or breathlessness during the last 12 months?	HUNT- main questionnaire
Chronic bronchitis	Have you had a cough with phlegm for periods of at least 3 months during each of the last two years?	HUNT- main questionnaire
Cough phlegm	Do you usually bring up phlegm when coughing?	HUNT- main questionnaire
Cough daily	Do you cough daily during periods of the year?	HUNT- main questionnaire

3.4.5 Self-reported asthma, doctor-diagnosed COPD, and respiratory symptoms

We included self-reported asthma, doctor-diagnosed COPD, and respiratory symptoms such as wheezing/dyspnoea last year (LY), chronic bronchitis, cough phlegm, and cough daily The English translation of the questions used in the study can be found in Table 4.

3.4.6 Covariates

We collected information on covariates from clinical examinations and questionnaires in the HUNT2 and the HUNT3.

Age in years was recorded to one decimal place. Sex was recorded as men or women. Region of residence was recorded as urban or rural residence. Height and weight were measured with light clothing and without shoes, and rounded to the nearest centimetre or half kilogram, respectively [129]. Body mass index was calculated as weight (kg) divided by squared height (m^2). Smoking status was recorded as never smoked, Ex-smoker daily, or current smoker daily. Smoking pack-years was recorded as number of packets of cigarette per year. Physical activity was recorded as light and hard exercise daily. For light exercise, people were asked to report their "Average of hours of low physical activity per week in the last year?" For hard exercise, people were asked to report their "Average of hours of vigorous physical activity per week in the last year?" Both light and hard exercise were recorded as none, less than 1 hour, 1-2 hours, or 3 hours or more. The highest level of education was recorded as "primary school 7-10 years, continuation school, folk high school", "university qualifying examination, junior college, A levels", "university or other post-secondary education, less than 4 years", or "university/college, 4 years or more". Self-reported diabetes ever was recorded. Self-reported asthma ever was recorded. Cardiovascular disease included self-reported angina pectoris, myocardial infarction, and stroke. Based on automatic oscillometric method, systolic blood pressure was measured three times and the mean of the last two measurements was used [129, 130]. Applying the enzymatic colorimetric cholesterol esterase method, the non-fasting total serum cholesterol (mmol/L) was measured [129, 130].

3.4.7 Outcomes

The outcomes studied were all-cause mortality and the first unplanned hospitalization due to COPD. COPD hospitalizations were identified from the international statistical classification of disease and related health problems (ICD) codes in medical records and the codes used are presented in Table 5 [9]. Information on date of death and/or COPD hospitalization was obtained from the Norwegian Cause of Death Registry and The Nord-Trøndelag Hospital Trust, respectively.

Table 5. Lists of ICD codes for COPD hospitalizations among people with COPD.

	ICD-10	**ICD-9**
*- Primary diagnosis	Bronchitis, not specified as acute or chronic * *J40*	Chronic airway obstruction, not elsewhere classified * *496*
	Simple and mucopurulent chronic bronchitis * *J41*	Bronchitis, not specified as acute or chronic * *490*
	Unspecified chronic bronchitis * *J42*	Bronchitis, not specified as acute or chronic * *490*
	Emphysema * *J43*	Emphysema * *492*
	Other chronic obstructive pulmonary disease (COPD) * *J44*	Chronic bronchitis * *491*
#- Primary diagnosis but in combination with a secondary diagnosis of J40-J44 from ICD-10 or 490-492 and 496 from ICD-9	Influenzas # *J09, J10, J11*	Influenzas # *487, 488*
	Pneumonias # *J12 – J18*	Pneumonias # *480 – 486*
	Dyspnoea # *R06.0*	Shortness of breath # 786.05
	Acute bronchitis # *J20*	Acute bronchitis # *466.0*
	Unspecified acute lower respiratory infection # *J22*	
	Respiratory failure, not elsewhere classified # *J96*	Respiratory failure # *518.81, 518.83, 518.84*

3.4.7.1 Norwegian Cause of Death Registry

The Norwegian Cause of Death Registry is one of the registries under the vital registration system in Norway. This registry contains digitalized information on cause of death and date since 1951 [141]. The information of date of death are collected as well as age, sex, cause, place of death, and place of residence in Norway. This registry covers all deaths in Norway, regardless of whether the deceased are registered inhabitants of Norway or not. Norwegians who die abroad are also registered in the system [141, 142]. This registry used to be maintained by Statistics Norway, but since 2011 the Norwegian Institute of Public Health (NIPH) has processed data for the registry. In 2014, the NIPH became sole responsible for maintaining the registry [141].

This registry is based on the death certificate prepared by doctors in Norway. The death certificate follows the ICD codes for the classification of cause of death. In 1996, the 10th revision of ICD was implemented in Norway [142]. The implementation of ICD helps to compare mortality data with other countries. The cause of deaths was recorded manually until 2005. Then, the Automated Classification of Medical Entities (ACME) computer program was introduced [141, 142]. The program uses all the death certificates to select the underlying cause of death according to the ICD codes. For the validation of the data, the cause of death on the death certificate is examined and controlled to check if it is plausible for a person of the specified age and sex [142].

3.4.7.2 Nord-Trøndelag Hospital Trust

The Nord-Trøndelag Hospital Trust [143] is a trust, which manages the patient administrative systems and electronic patient journals of Levanger and Namsos hospitals in the former Nord-Trøndelag County. These are the only hospitals in the county. The Nord-Trøndelag Hospital Trust manages large amounts of data. Some of these data are used in health-promotion research and

quality work. They have been managing data from the hospitals since their establishment. Mainly, they have managed data that relate to the patient's hospital stay, admission, or clinical visits. Coding secretaries check the ICD codes related to the patient's hospital stay and/or clinical visits, regularly. All provision of data to be used in research is according to Norwegian law and General Data Protection Regulation.

3.4.8 Follow-up

Follow-up for both events (all-cause mortality and COPD hospitalization) began at the date of participation in the HUNT2 and ended at an event date or at the end of follow-up, 31 December 2015. Observations were right-censored on emigration. When COPD hospitalization was the event, observations were also right-censored at the date of death. There was no other loss to follow-up.

3.5 Statistical analysis

3.5.1 Paper I

In Paper I, we presented numbers and percentage (%) for categorical variables and mean and standard deviation (SD) for continuous variables. The prevalence (%) and 95% confidence intervals (CI) of fixed-ratio COPD and LLN COPD were calculated. Pearson's chi-square test was used for the comparison of proportions between groups.

Generalized Estimation Equation (GEE) models were used to assess the changes in prevalence as odds ratios (ORs) with 95% CI. The GEE models with unstructured correlation matrices were used to account for 37.7% repeated participants in the HUNT2 and the HUNT3 [21]. From HUNT2 to HUNT3, the crude and adjusted relative changes for COPD, GOLD grades, ABCD groups, and respiratory symptoms were calculated. Models were adjusted for age, sex, and smoking (never, former, current; missing 1.9% in the HUNT2 and 2.8% in the HUNT3).

The 11-year cumulative incidence of COPD with 95% CI and annual mean decline in FEV_1 were calculated among participants attending both the HUNT2 and the HUNT3 and free from COPD at the HUNT2.

Multiple imputations (10 imputed datasets) were used to account for missing values of covariates [22].

Sample weighting

There were unequal selection probabilities and loss to follow-up during sampling. To account for these issues and to generalize our finding to the population of Nord-Trøndelag, we weighted our

analysis. The weighting was based on the inverse probability of selection to the HUNT Lung Study [23] and the predicted probability of response in the HUNT [8, 24].

For the weighting, firstly, the inverse of predicted probability of response was used to adjust for sample loss due to non-response to the HUNT. A logistic model stratified by sex (men, women) was developed separately for the HUNT2 and the HUNT3 to calculate the predicted probability of response for those who participated among invited in these two studies where age (categorized in 10 years interval), marital status (unmarried, married, widow/widower, divorced), and region of residence (rural, urban municipalities) were included as independent variables. Secondly, the inverse probability of selection was used to adjust for sample loss due to the sampling and exclusion criteria. The symptom sample and those meeting the symptom criteria from the random sample were given a weight of 1. The remaining random sample were given a weight based on the probability of selection (weight = number of participants in the HUNT divided by number of participants with acceptable spirometry in the HUNT Lung Study) (Figure 6 and 7).

As a sensitivity analysis, results from random samples only were calculated.

3.5.2 Paper II

In Paper II, we calculated the mortality rates per 1000 person-years with 95% CI. The cumulative survival curves for mortality were constructed based on Kaplan-Meier estimates.

We used Cox proportional hazard models to assess the associations of pre-BD and post-BD lung function with mortality. In the Cox models, time since enrolment was used as the time axis. The HRs and 95% CI were calculated for crude (Model 1) and adjusted models (Model 2). Model 2 was adjusted for age (as a continuous variable), sex (women, men), smoking [never, former (<10, 10-19, ≥20 pack-years), current (<10, 10-19, ≥20 pack-years), unknown], body mass index (<25.0, 25.0-29.9, ≥30.0, unknown), and education (<10, ≥10 years, unknown). Additionally, in supplementary analyses, the models (Model 3) were adjusted for physical activity (none, light exercise, hard exercise, unknown), cardiovascular diseases (no, yes, unknown), asthma ever (no, yes, unknown), diabetes ever (no, yes, unknown), systolic blood pressure (sex-specific quartiles, unknown), and cholesterol (sex-specific quartiles, unknown).

Proportional hazard assumptions were evaluated using log-log survival curves and Schoenfeld residuals tests [144]. Multicollinearity was tested where the variance inflation factor (VIF) was less than 1.5 in all models [145, 146]. As a measure of goodness of fit, we estimated the Akaike information criteria (AIC) and performed Gronnesby and Borgan tests for each model [147, 148].

Time-dependent AUCs were used to compare the discrimination ability of pre-BD and post-BD lung function to predict mortality [149-152]. The incident/dynamic (I/D) AUC and cumulative dynamic (C/D) AUC were two approaches used for the time-dependent AUC. The I/D AUC models account for incident cases at time t and dynamic control, which means it characterizes the time-varying performance without selecting a particular timeframe over which cases accrue, whereas C/D AUC models account for cumulative cases at time t and dynamic control [151, 153]. We compared the AUCs for crude lung function models because a clinical decision usually does not explicitly take other factors into account [52, 121]. Additionally, we calculated the Concordance Index (C-index) as a global measure of informativeness. The C-index is a weighted average of I/D AUC [151]. We used 10,000 bootstrap iterations to calculate 95% CI for I/D AUC and C-index [153]. A general bootstrap algorithm (gBA) with 10,000 bootstrap iterations was applied to compare the I/D AUC and C-index [154].

We performed all the analyses both among people with airflow limitation and among people with COPD.

3.5.3 Paper III

In Paper III, the methods used were similar to Paper II.

In addition, we treated the GOLD classification as continuous measures to test for trend. We used survival analysis and I/D AUC to calculate the discrimination abilities of the GOLD classification to predict mortality and COPD hospitalization.

3.5.4 Paper IV

In Paper IV, the methods used were similar to Paper II.

In addition, we treated the classifications of COPD severity as continuous measures to test for trend. We used survival analysis and I/D AUC to calculate the discrimination abilities of a range of lung function measures and their respective methods of classification of COPD severity to predict mortality and COPD hospitalization.

3.5.5 Software

Statistical analysis was performed using R 3.5.0 (http://www.r-project.org) and Stata 15.1 (StataCorp., College Station, Texas).

3.6 Ethics

The participants in the HUNT2 and the HUNT3 signed informed written consent for the use of their data in research. This project has been approved by the Regional Committee for Medical and Health Research Ethics (2015/1461/REK midt).

4. Results

4.1 Paper I

We estimated the prevalence and trend of COPD among 7158 adults in the HUNT2 and 8788 adults in the HUNT3 aged ≥40 years old. The estimates were weighted to the population of 59,006 in the HUNT2 and 63,830 in the HUNT3 aged ≥40 years old. As a sensitivity analysis, the estimates were calculated in random sample of 1807 in the HUNT2 and 2646 in the HUNT3 aged ≥40 years old. The weighted estimates were similar in random samples.

The estimated prevalence of COPD decreased from HUNT2 (16.7%) to HUNT3 (14.8%) (Table 6) using the fixed-ratio criteria. A similar decrease was observed from HUNT2 (10.4%) to HUNT3 (7.3%) using the LLN criteria (Table 6). Among men, the prevalence of COPD decreased from HUNT2 (21.2%) to HUNT3 (16.6%) but it remained relatively stable in women (HUNT2 12.4%, HUNT3 13.0%) using fixed-ratio criteria (Table 6). The difference in prevalence between men and women reduced from the HUNT2 to HUNT3 (Table 6).

Among 2202 people free from COPD at the HUNT2 and participating in the HUNT3, the cumulative incidence of COPD was 9.7% (men 11.9%, women 7.9%) using the fixed-ratio criteria over the 11-year period. Using LLN criteria the estimates was 3.0% (men 3.3%, women 2.7%).

The prevalence of asthma ever, wheezing/dyspnoea last year, chronic bronchitis in last two years, cough phlegm, and cough daily last year increased from HUNT2 to HUNT3 (Figure 9).

Table 6. Estimated weighted prevalence of COPD using fixed-ratio ($FEV_1/FVC<0.70$) and LLN criteria by GLI-2012 among people aged ≥40 years in the HUNT.

Characteristic	Diagnostics Methods	1995-1997 (HUNT2) (n=7158)	2006-2008 (HUNT3) (n=8788)	Absolute change in prevalence	Crude relative change in prevalence using GEE	Adjusted relative change in prevalence using GEE
		% (95% CI)	% (95% CI)	(%)	OR, (95% CI) [€]	OR, (95% CI) [#€]
Men	$FEV_1/FEV<0.70$	21.2 (18.8-23.7)	16.6 (15.0-18.3)	- 4.6	0.92(0.78-1.08)	0.95(0.79-1.15)
	$FEV_1/FVC<LLN$*	13.0 (11.2-15.1)	7.7 (6.7-8.8)	- 5.3	0.64(0.52-0.78)	0.72(0.57-0.90)
Women	$FEV_1/FEV<0.70$	12.4 (10.7-14.3)	13.0 (11.7-14.6)	+ 0.6	1.05(0.86-1.27)	0.94(0.76-1.17)
	$FEV_1/FVC<LLN$*	8.0 (6.7-9.5)	6.9 (6.0-7.9)	- 1.1	0.80(0.64-0.99)	0.85(0.67-1.08)
Overall	$FEV_1/FEV<0.70$	16.7 (15.2-18.2)	14.8 (13.7-16.0)	- 1.9	0.96(0.85-1.09)	0.93(0.81-1.07)
	$FEV_1/FVC<LLN$*	10.4 (9.3-11.7)	7.3 (6.6-8.0)	- 3.1	0.70(0.60-0.81)	0.76(0.65-0.89)

Abbreviations: CI (confidence interval); FEV_1 (forced expiratory volume in the first second); FVC (forced vital capacity); GEE (Generalized Estimation Equation); GLI (global lung function initiative); HUNT (Nord-Trøndelag Health Study); LLN (lower limit of normal); OR (odds ratio)

[€]- accounting for overlapping people in HUNT2 and HUNT3; [#]- multiple imputation of missing information and adjustment of age, sex (men, women), smoking (never, previous, current); *- people with missing predicted values are excluded.

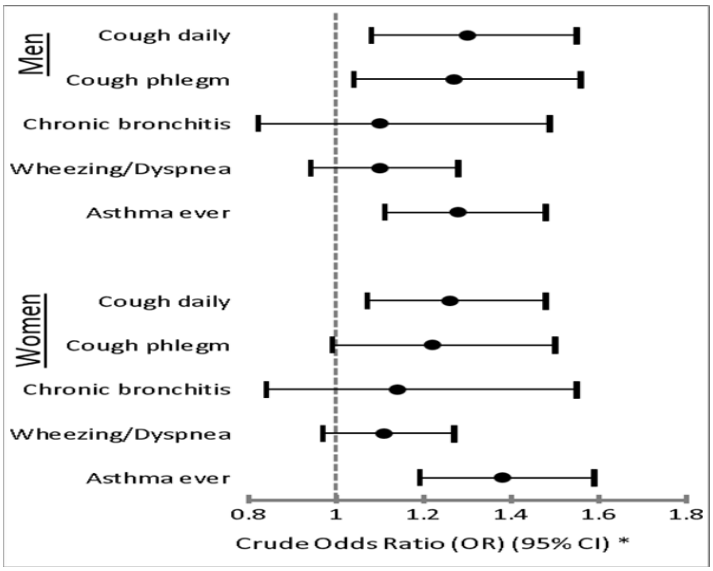


Figure 9. The crude relative change in weighted prevalence of self-reported asthma ever and respiratory symptoms from HUNT2 to HUNT3 using GEE models among people aged ≥40 years.
*Crude relative change in weighted prevalence of self-reported asthma ever and respiratory symptoms using GEE (generalized estimation equation) models accounting for overlapping people in HUNT2 (1995-1997) and HUNT3 (2006-2008)

4.2 Paper II

We investigated the discrimination ability of pre-BD and post-BD lung function in predicting mortality among 2538 people with airflow limitation and 1262 people with COPD aged ≥40 years old over a 20-year follow-up.

In the cohort of people with airflow limitation, 1387 people died over 20.4 years of follow-up. The majority were men (57.6%), older (median=63.7 years, mean=62.6 years, interquartile range=18.6 years), and 41.3% were current smokers.

A 10% reduction in $ppFEV_1$ and 1-unit reduction in FEV_1 z-score and FEV_1Q were associated with 19%, 36%, and 33% increased risk of death using pre-BD lung function, respectively (Table 7, Model 2). The corresponding results for post-BD lung function were 22%, 41%, and 38%. Similarly, worsening modified-GOLD categories were associated with increased risk for death (Table 7, Model 2). Similar results were observed in Model 3 (Supplementary section).

Among people with airflow limitation, post-BD had higher I/D AUC than pre-BD in predicting mortality using $ppFEV_1$ (pre-BD 60.8, post-BD 61.8), FEV_1 z-score (pre-BD 58.5, post-BD 60.4), FEV_1Q (pre-BD 68.7, post-BD 70.1), and modified-GOLD categories (pre-BD 62.3, post-BD 64.5) at 20 years of follow-up (Table 8, Figure 10). Similar results were observed over the follow-up time (Figure 10).

Among people with COPD, post-BD had better discrimination ability than pre-BD, except for GOLD grades where post-BD and pre-BD had similar discrimination ability to predict mortality (p=0.268) (Figure 11).

The results from C-index and C/D AUC were generally in agreement with I/D AUC.

Table 7. Hazard ratios for pre-BD and post-BD lung function for all-cause mortality among people aged ≥40 years with airflow limitation in the HUNT2 (1995-1997).

Lung function (n=2538)		Pre-BD		Post-BD	
		HR (95% CI) *	HR (95% CI) [#]	HR (95% CI) *	HR (95% CI) [#]
$ppFEV_1$ [§]		1.28 (1.24-1.31)	1.19 (1.16-1.22)	1.31 (1.27-1.34)	1.22 (1.19-1.25)
FEV_1 z-score [†]		1.31 (1.26-1.37)	1.36 (1.30-1.42)	1.40 (1.34-1.45)	1.41 (1.35-1.48)
FEV_1Q [¥]		1.67 (1.61-1.73)	1.33 (1.27-1.39)	1.72 (1.66-1.78)	1.38 (1.32-1.44)
modified-GOLD categories [¶]	Normal	Reference	Reference	Reference	Reference
	PRISm	2.33 (1.85-2.94)	1.79 (1.41-2.26)	2.59 (2.08-3.24)	1.95 (1.56-2.45)
	Mild obstructive	1.77 (1.47-2.12)	1.17 (0.98-1.41)	2.12 (1.80-2.50)	1.16 (0.98-1.37)
	Moderate obstructive	2.78 (2.38-3.25)	1.78 (1.52-2.08)	3.20 (2.78-3.69)	1.86 (1.60-2.15)
	Severe obstructive	5.23 (4.32-6.33)	2.77 (2.27-3.37)	6.59 (5.41-8.02)	3.44 (2.80-4.23)
	Very severe obstructive	7.00 (5.02-9.75)	5.03 (3.57-7.08)	6.00 (3.73-9.67)	4.68 (2.89-7.59)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GOLD (global initiative for chronic obstructive lung disease), GLI (Global Lung Function Initiative), HR (Hazard ratio), CI (confidence interval), BD (bronchodilator), PRISm (preserved ratio impaired spirometry),

*- Model 1 (crude) [#]- Model 2 - adjusted for age, sex, smoking, body mass index, education

[§] – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. HRs were for a 10% reduction in $ppFEV_1$.

[†] – forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. HRs were for a 1-unit reduction in FEV_1 z-score.

[¥] - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. HRs were for a 1-unit reduction in FEV_1Q.

[¶] - normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent-predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & $ppFVC < 80$; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table 8. Incident/Dynamic time-dependent AUCs for pre-BD and post-BD lung function for all-cause mortality at 20 years of follow-up among people aged ≥40 years with airflow limitation in the HUNT2 (1995-1997).

Lung function (n=2538)	Pre-BD	Post-BD	p value
	I/D AUC (95% CI) *	I/D AUC (95% CI) *	
$ppFEV_1$ [§]	60.8 (59.3-62.2)	61.8 (60.2-63.4)	0.005
FEV_1 z-score [†]	58.5 (57.0-59.9)	60.4 (58.8-62.0)	<0.001
FEV_1Q [¥]	68.7 (66.8-70.5)	70.1 (68.1-72.1)	0.002
modified-GOLD categories [¶]	62.3 (60.6-63.8)	64.5 (62.9-66.1)	<0.001

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), AUC (area under receiver operating characteristics curves), BD (bronchodilator), PRISm (preserved ratio impaired spirometry)

*- Model 1 (crude) - the Cox model included pre-BD or post-BD lung function.

[§] – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation.

[†]- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation.

[¥] - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution

[¶] - normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent-predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & $ppFVC < 80$; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

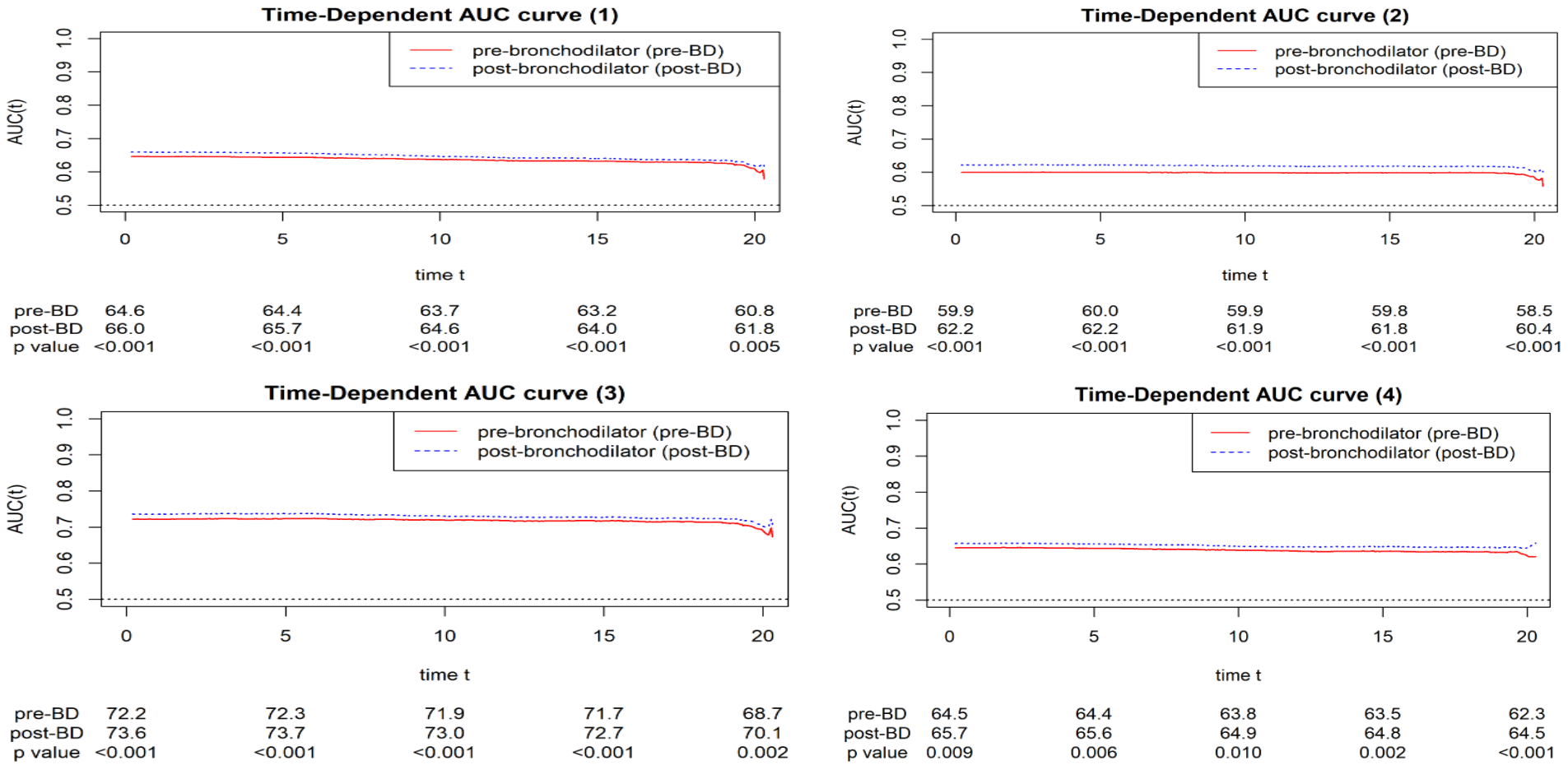


Figure 10. Incident/Dynamic time-dependent AUC curves for pre-BD and post-BD (1) percent-predicted FEV_1, (2) FEV_1 z-score, (3) FEV_1Q, and (4) modified-GOLD categories for all-cause mortality over the follow-up time (years) among people aged ≥40 years with airflow limitation in the HUNT2 (1995-1997).

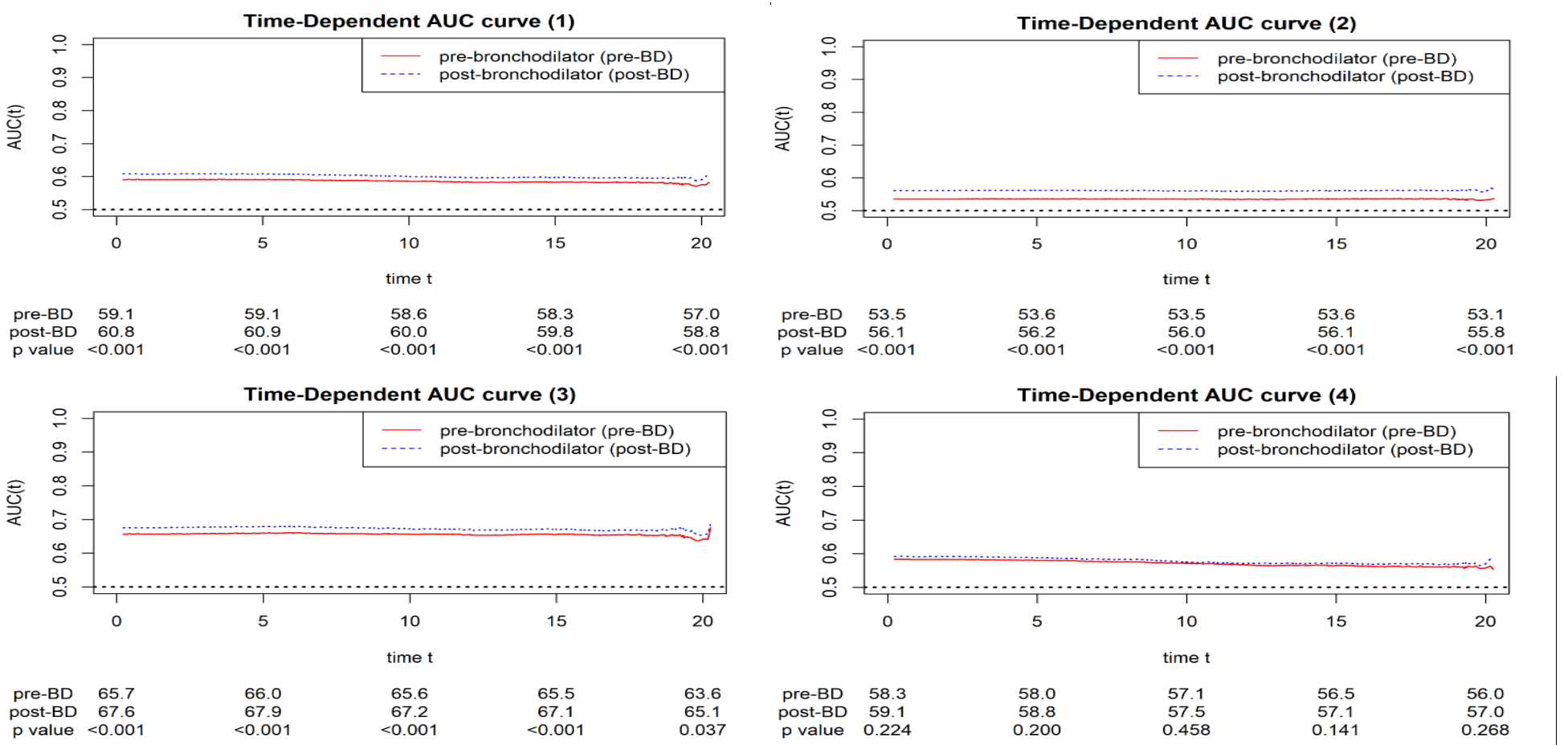


Figure 11. Incident/Dynamic time-dependent AUC curves for pre-BD and post-BD (1) percent-predicted FEV_1, (2) FEV_1 z-score, (3) FEV_1Q, and (4) GOLD grades for all-cause mortality over the follow-up time (years) among people aged ≥40 years with COPD in the HUNT2 (1995-1997).

4.3 Paper III

We compared the discrimination abilities of the GOLD 2007, GOLD 2011, and GOLD 2017 classifications to predict mortality and COPD hospitalization among 1300 people with COPD aged ≥40 years old over a 20-year follow-up.

In this population-based COPD cohort with over 20.4 years of follow-up, 896 people died and 522 were hospitalized due to COPD. The majority of people with COPD were men (62.9%), older (median=66.9 years, mean=65.6 years, interquartile range=15.8 years), and 47.9% were current smokers.

Using the GOLD 2007 classification, 31.9%, 54.2%, 12.5%, and 1.4% were classified as grades 1-4, respectively. The GOLD 2011 classification increased the proportion of people in the lowest category (group A) to 59.3%. This was further increased to 65.1% in group A under the GOLD 2017 classification. The number of people in the highest two categories was slightly higher using the GOLD 2011 (16.8 % in groups C or D) than the GOLD 2007 (13.9% in grades 3 or 4) but considerably lower using the GOLD 2017 (4.1% in groups C or D) (Figure 12).

In adjusted models, worsening categories of the GOLD 2007, GOLD 2011, or GOLD 2017 classifications were associated with increased risk for death and COPD hospitalization ($p_{trend}<0.001$), except for risk of death associated with the GOLD 2017 classification ($p_{trend}=0.114$) (Table 9, Model 2). Similar results were observed in Model 3 (Supplementary section).

The AUCs for mortality at 20 years of follow-up for the GOLD 2007, GOLD 2011, and GOLD 2017 classification were 57.0, 54.1, and 52.6, respectively. The corresponding estimates for COPD hospitalization were 63.1, 60.9, and 56.1 (Table 10, Figure 13). The results were similar over the follow-up time (Figure 13).

Table 9. Hazard ratios for GOLD 2007, GOLD 2011, and GOLD 2017 among people with COPD aged ≥40 years in the HUNT2 (1995-1997).

Outcomes	GOLD categories	GOLD classifications (n=1300)					
		GOLD 2007 ¶		GOLD 2011 ¥		GOLD 2017 †	
		HR (95% CI) *	HR (95% CI) #	HR (95% CI) *	HR (95% CI) #	HR (95% CI) *	HR (95% CI) #
All-cause mortality	grade 1/ group A	Reference	Reference	Reference	Reference	Reference	Reference
	grade 2/ group B	1.51 (1.29-1.76)	1.56 (1.33-1.82)	1.10 (0.93-1.29)	1.03 (0.87-1.21)	1.21 (1.05-1.39)	1.16 (1.01-1.34)
	grade 3/ group C	3.13 (2.54-3.86)	2.88 (2.32-3.58)	2.21 (1.75-2.78)	1.74 (1.38-2.20)	1.39 (0.87-2.22)	1.16 (0.72-1.86)
	grade 4/ group D	2.95 (1.80-4.84)	3.87 (2.34-6.39)	1.84 (1.48-2.28)	2.04 (1.63-2.55)	0.79 (0.49-1.26)	1.05 (0.65-1.69)
COPD hospitalization	grade 1/ group A	Reference	Reference	Reference	Reference	Reference	Reference
	grade 2/ group B	2.15 (1.72-2.69)	2.05 (1.63-2.57)	1.41 (1.14-1.75)	1.42 (1.14-1.76)	1.64 (1.36-1.96)	1.64 (1.36-1.97)
	grade 3/ group C	6.40 (4.87-8.41)	5.11 (3.85-6.78)	3.89 (2.95-5.14)	3.21 (2.42-4.27)	3.27 (1.97-5.41)	3.17 (1.88-5.32)
	grade 4/ group D	22.56 (13.19-38.57)	17.08 (9.77-29.86)	4.09 (3.18-5.26)	3.75 (2.88-4.88)	2.01 (1.26-3.20)	2.15 (1.33-3.46)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GOLD (global initiative for chronic obstructive lung disease), HR (Hazard ratio), CI (confidence interval)

*- Model 1 (crude) #- Model 2 - adjusted for age, sex, smoking, body mass index, education

¶ - grade 1 – percent predicted forced expiratory volume in first second ($ppFEV_1$) ≥80; grade 2 –80>$ppFEV_1$≥50; grade 3 –50>$ppFEV_1$≥30; grade 4 –$ppFEV_1$<30

¥ - group A – $ppFEV_1$≥50 and exacerbation history <2 and modified Medical Research Council dyspnoea scale (mMRC) <2; group B – $ppFEV_1$≥50 and exacerbation history <2 and mMRC ≥2; group C – $ppFEV_1$<50 or exacerbation history ≥2 and mMRC <2; group D – $ppFEV_1$<50 or exacerbation history ≥2 and mMRC ≥2

†- group A – mMRC <2 & exacerbation history <2; group B – mMRC ≥2 & exacerbation history <2; group C – mMRC <2 & exacerbation history ≥2; group D – mMRC ≥2 & exacerbation history ≥2

Table 10. AUCs for GOLD 2007, GOLD 2011, and GOLD 2017 at 20 years of follow-up among people with COPD aged ≥40 years in the HUNT2 (1995-1997).

Outcomes	GOLD classifications (n=1300)		
	GOLD 2007 ¶	GOLD 2011 ¥	GOLD 2017 †
	AUC (95% CI) *****	AUC (95% CI) *****	AUC (95% CI) *****
All-cause mortality	57.0 (54.8-59.1)	54.1 (52.1-56.0)	52.6 (51.0-54.3)
COPD hospitalization	63.1 (58.7-66.9)	60.9 (56.1-64.4)	56.1 (54.0-58.1)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997); AUC (area under receiver operating characteristics curves)

*- Model 1 (crude model)- the Cox model included GOLD 2007, GOLD 2011, or GOLD 2017.

¶ - grade 1 – percent predicted forced expiratory volume in first second ($ppFEV_1$) ≥80; grade 2 –80>$ppFEV_1$≥50; grade 3 –50>$ppFEV_1$≥30; grade 4 –$ppFEV_1$<30

¥ - group A – $ppFEV_1$≥50 and exacerbation history <2 and modified Medical Research Council dyspnoea scale (mMRC) <2; group B – $ppFEV_1$≥50 and exacerbation history <2 and mMRC ≥2; group C – $ppFEV_1$<50 or exacerbation history ≥2 and mMRC <2; group D – $ppFEV_1$<50 or exacerbation history ≥2 and mMRC ≥2

†- group A – mMRC <2 & exacerbation history <2; group B – mMRC ≥2 & exacerbation history <2; group C – mMRC <2 & exacerbation history ≥2; group D – mMRC ≥2 & exacerbation history ≥2

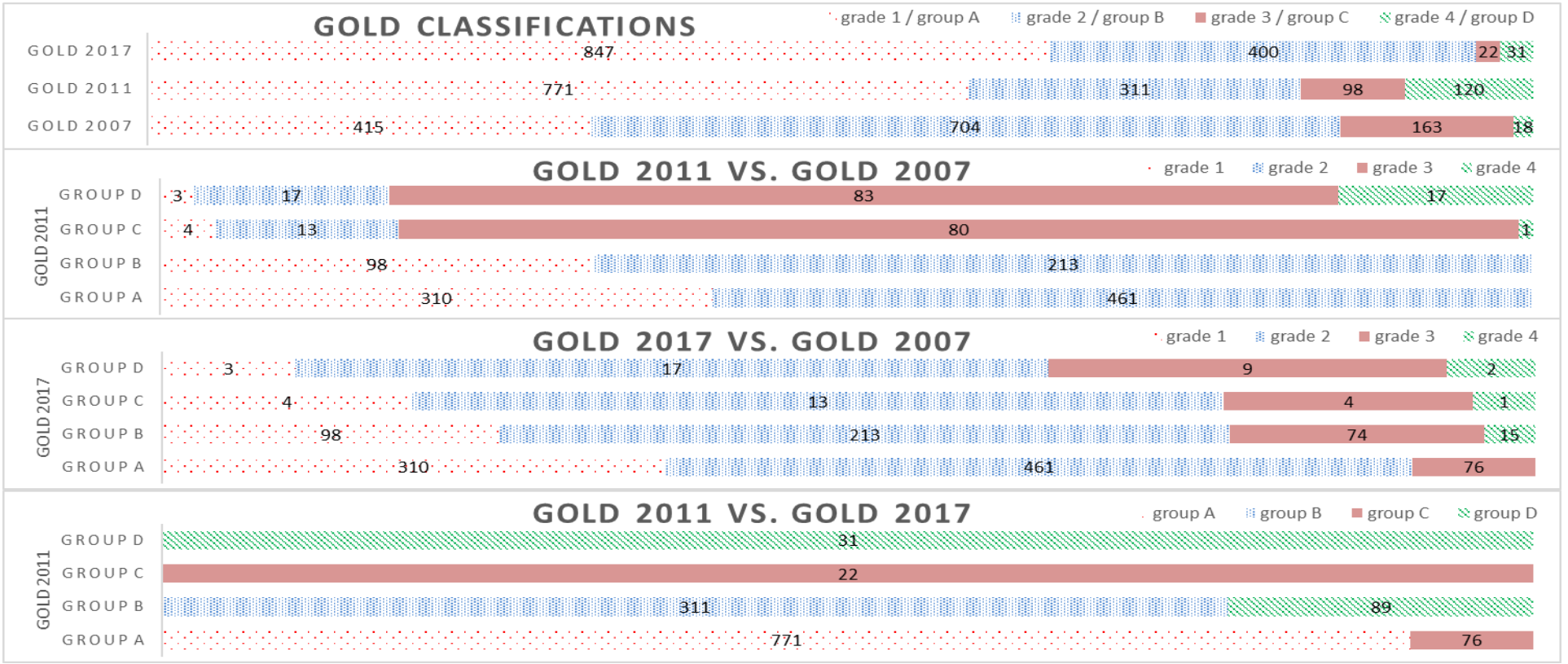
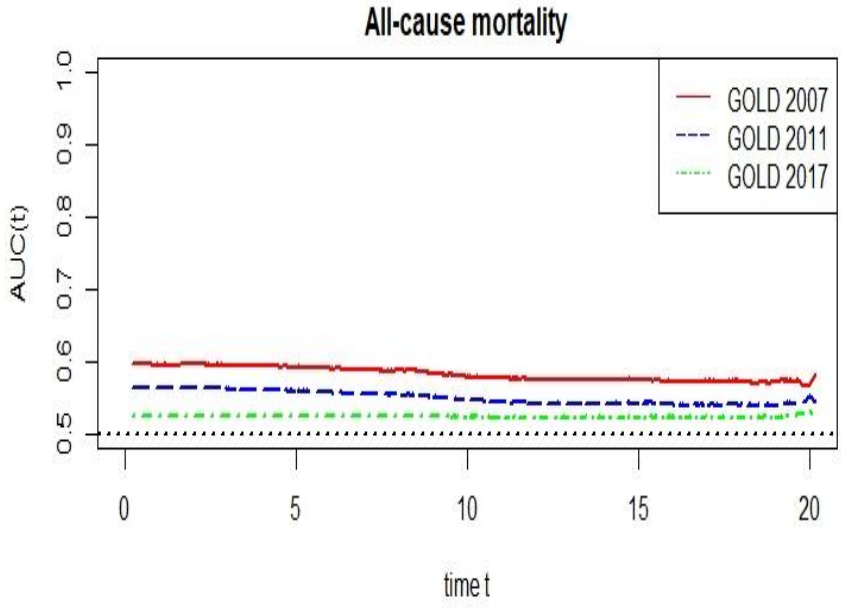
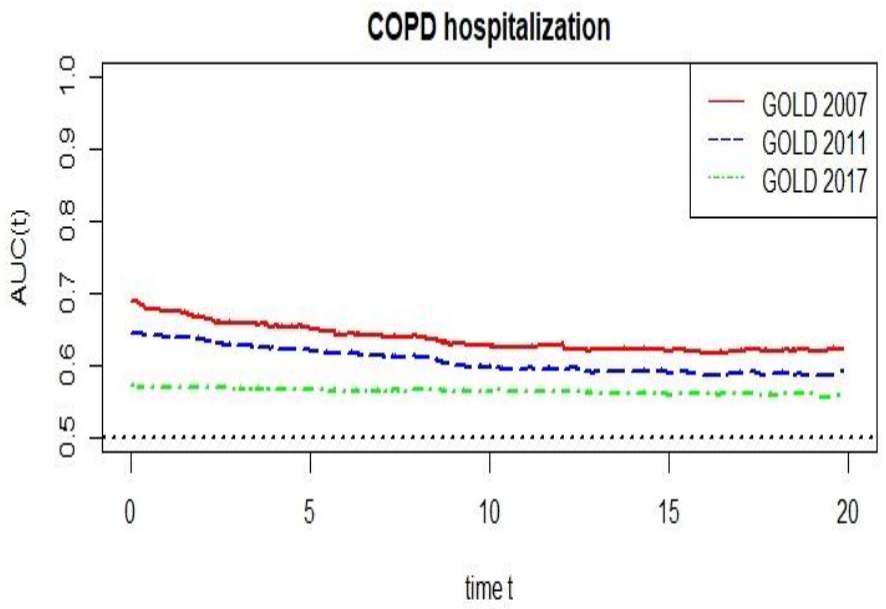


Figure 12. Distribution of people in different GOLD classifications.





GOLD 2007	59.7	59.3	57.9	57.5	57.0
GOLD 2011	56.4	56.0	54.8	54.3	54.1
GOLD 2017	52.5	52.5	52.4	52.4	52.6
07vs11(p value)	<0.001	<0.001	<0.001	<0.001	0.002
07vs17(p value)	<0.001	<0.001	<0.001	<0.001	0.001
11vs17(p value)	0.002	0.002	0.011	0.019	0.182

GOLD 2007	68.9	65.4	62.7	62.1	63.1
GOLD 2011	64.4	62.2	59.8	59.1	60.9
GOLD 2017	57.1	56.7	56.5	56.0	56.1
07vs11(p value)	<0.001	<0.001	<0.001	<0.001	0.244
07vs17(p value)	<0.001	<0.001	<0.001	<0.001	0.002
11vs17(p value)	<0.001	<0.001	<0.001	<0.001	0.017

Figure 13. AUC curves for GOLD 2007, GOLD 2011, and GOLD 2017 for all-cause mortality and COPD hospitalization over the follow-up time (years) among people aged ≥40 years with COPD in the HUNT2 (1995-1997).

4.4 Paper IV

We compared the discrimination abilities of different lung function measures and their respective methods of classification of COPD severity to predict mortality and COPD hospitalization among 890 people with COPD aged ≥40 years old over a 20-year follow-up.

In this population-based COPD cohort with over 20.4 years of follow-up, 615 people died and 428 were hospitalized due to COPD. The majority of people with COPD were men (60.4%), older (median=65.2 years, mean=63.8 years, interquartile range=17.1 years), and current smokers (53.3%).

In adjusted models, worsening quartiles of $ppFEV_1$, FEV_1 z-score, $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q were associated with increased risk for death and COPD hospitalization ($p_{trend}<0.001$ for all measures) (Table 11, Model 2). Similar results were observed in Model 3 (Supplementary section).

In crude models, the AUC for FEV_1Q (68.3) was higher than $ppFEV_1$ (61.9), FEV_1 z-score (57.9), $FEV_1.Ht^{-2}$ (66.8), and $FEV_1.Ht^{-3}$ (66.6) to predict mortality at 20 years of follow-up (Table 12, Figure 14). Similar results were observed for COPD hospitalization (Table 12; Figure 14) and over the follow-up time (Figure 14).

In crude models, the AUC for FEV_1Q quartiles (67.2) were higher than $ppFEV_1$ quartiles (63.3), GOLD grades (60.4), ATS/ERS grades (61.9), FEV_1 z-score quartiles (59.2), FEV_1 z-score grades (58.5), $FEV_1.Ht^{-2}$ quartiles (65.2), and $FEV_1.Ht^{-3}$ quartiles (66.6) to predict mortality at 20 years of follow-up (Table 12; Figure 15). Similar results were observed for COPD hospitalization (Table 12; Figure 15) and over the follow-up time (Figure 15).

Table 11. Hazard ratios for ppFEV$_1$, FEV$_1$ z-score, FEV$_1$.Ht^{-2}, FEV$_1$.Ht^{-3}, and FEV$_1$Q quartiles among people with COPD aged ≥40-year in the HUNT2 (1995-1997).

Outcome	Lung function Quartiles	Lung function (n=890)				
		ppFEV$_1$ ¶	FEV$_1$ z-score §	FEV$_1$.Ht^{-2} ǂ	FEV$_1$.Ht^{-3} ¥	FEV$_1$Q †
		HR (95% CI)#	HR (95% CI)#	HR (95% CI)#	HR (95% CI)#	HR (95% CI)#
All-cause mortality	Quartile 1 (highest)	Reference	Reference	Reference	Reference	Reference
	Quartile 2	1.51 (1.17-1.95)	1.52 (1.19-1.93)	1.31 (0.98-1.74)	1.29 (0.97-1.71)	1.53 (1.14-2.06)
	Quartile 3	1.72 (1.33-2.22)	1.62 (1.27-2.06)	1.65 (1.24-2.21)	1.58 (1.18-2.11)	1.88 (1.40-2.53)
	Quartile 4 (lowest)	2.66 (2.07-3.42)	2.73 (2.15-3.48)	2.84 (2.11-3.83)	2.63 (1.95-3.53)	3.28 (2.41-4.46)
COPD hospitalization	Quartile 1 (highest)	Reference	Reference	Reference	Reference	Reference
	Quartile 2	1.37 (1.01-1.86)	1.32 (0.98-1.79)	1.58 (1.12-2.22)	1.40 (1.01-1.95)	1.72 (1.22-2.42)
	Quartile 3	1.71 (1.26-2.33)	1.53 (1.14-2.07)	2.09 (1.48-2.97)	2.01 (1.42-2.83)	2.58 (1.83-2.63)
	Quartile 4 (lowest)	3.69 (2.74-4.97)	3.70 (2.79-4.89)	4.72 (3.28-6.79)	3.88 (2.73-5.52)	5.09 (3.53-7.35)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GOLD (global initiative for chronic obstructive lung disease), HR (Hazard ratio), CI (confidence interval)

- Model 2: adjusted for age, sex, smoking, body mass index, education

¶ - percent-predicted forced expiratory volume in first second (ppFEV$_1$) based in GLI-2012 equation.

§ - forced expiratory volume in first second (FEV$_1$) z-score based on GLI-2012 equation.

ǂ - FEV$_1$ standardized by squared meter of height.

¥ - FEV$_1$ standardized by cubic meter of height.

† - FEV$_1$ standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV$_1$ distribution.

Table 12. AUCs for $ppFEV_1$ ($ppFEV_1$ quartiles, GOLD grades, ATS/ERS grades), FEV_1 z-score (FEV_1 z-score quartiles, FEV_1 z-score grades), $FEV_1.Ht^{-2}$ ($FEV_1.Ht^{-2}$ quartiles), $FEV_1.Ht^{-3}$ ($FEV_1.Ht^{-3}$ quartiles), and FEV_1Q (FEV_1Q quartiles) at 20 years of follow-up among people with COPD aged ≥40 years in the HUNT.

Outcomes	Lung function as continuous measures (n=890)							
	$ppFEV_1$ ¶			FEV_1 z-score §		$FEV_1.Ht^{-2}$ ǂ	$FEV_1.Ht^{-3}$ ¥	FEV_1Q †
	I/D AUC (95% CI) *			I/D AUC (95% CI) *		I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *
All-cause mortality	61.9 (58.9-64.6)			57.9 (55.4-60.5)		66.8 (62.6-70.4)	66.6 (62.5-70.1)	68.3 (64.0-72.1)
COPD hospitalization	67.9 (63.3-71.5)			65.4 (61.3-68.7)		71.3 (65.0-76.1)	70.7 (64.6-75.3)	72.7 (66.4-77.3)
Classification of COPD severity								
Outcomes	$ppFEV_1$ quartiles	GOLD grades	ATS/ERS grades	FEV_1 z-score quartiles	FEV_1 z-score grades	$FEV_1.Ht^{-2}$ quartiles	$FEV_1.Ht^{-3}$ quartiles	FEV_1Q quartiles
	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *	I/D AUC (95% CI) *
All-cause mortality	63.3 (60.3-65.7)	60.4 (56.6-63.7)	61.9 (58.5-64.5)	59.2 (56.5-61.6)	58.5 (56.0-60.6)	65.2 (62.0-68.1)	66.6 (62.8-69.5)	67.2 (63.3-70.3)
COPD hospitalization	65.7 (60.8-68.8)	61.4 (56.1-65.3)	62.4 (57.5-65.7)	63.7 (60.0-66.4)	62.5 (58.1-65.7)	65.1 (59.8-69.8)	64.9 (59.6-69.3)	66.8 (60.9-71.0)

Abbreviations: HUNT (Nord-Trøndelag Health Study); GOLD (global initiative for chronic obstructive lung disease); ATS/ERS (American Thoracic Society/European Respiratory Society), AUC (area under receiver operating characteristics curves)

*- Model 1: the crude Cox model included $ppFEV_1$, FEV_1 z-score, $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, FEV_1Q, $ppFEV_1$ quartiles, GOLD grades, ATS/ERS grades, FEV_1 z-score quartiles, FEV_1 z-score grades, $FEV_1.Ht^{-2}$ quartiles, $FEV_1.Ht^{-3}$ quartiles, or FEV_1Q quartiles

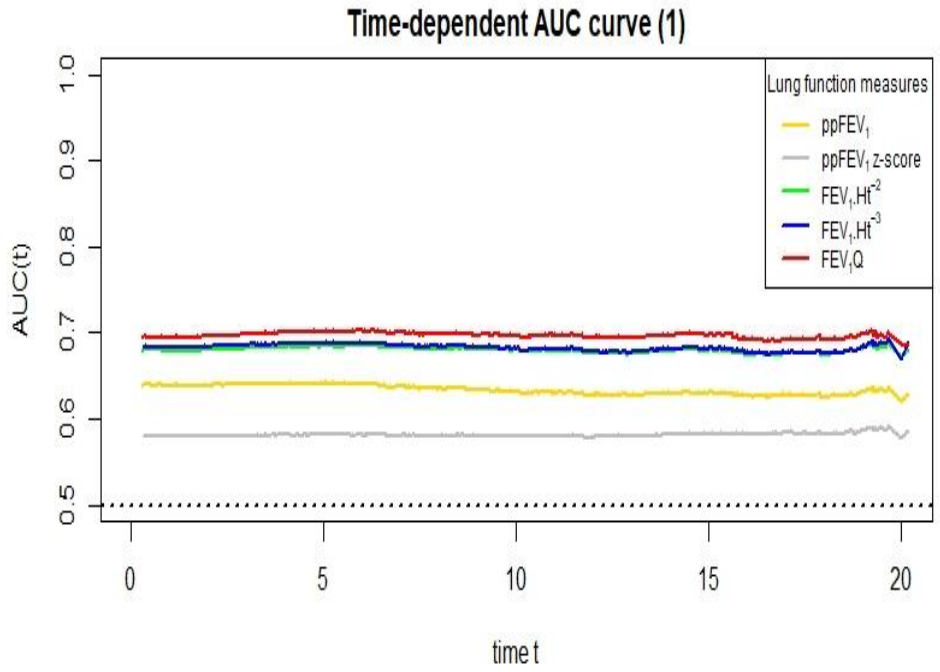
¶ - percent-predicted forced expiratory volume in first second ($ppFEV_1$) based in GLI-2012 equation.

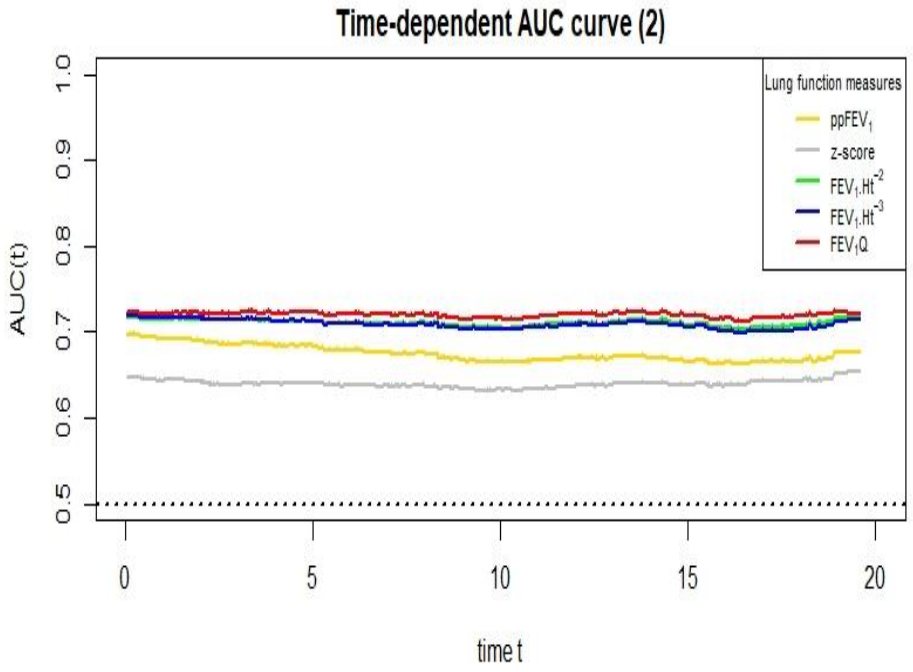
§ - forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation.

ǂ - FEV_1 standardized by squared meter of height.

¥ - FEV_1 standardized by cubic meter of height.

† - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution.

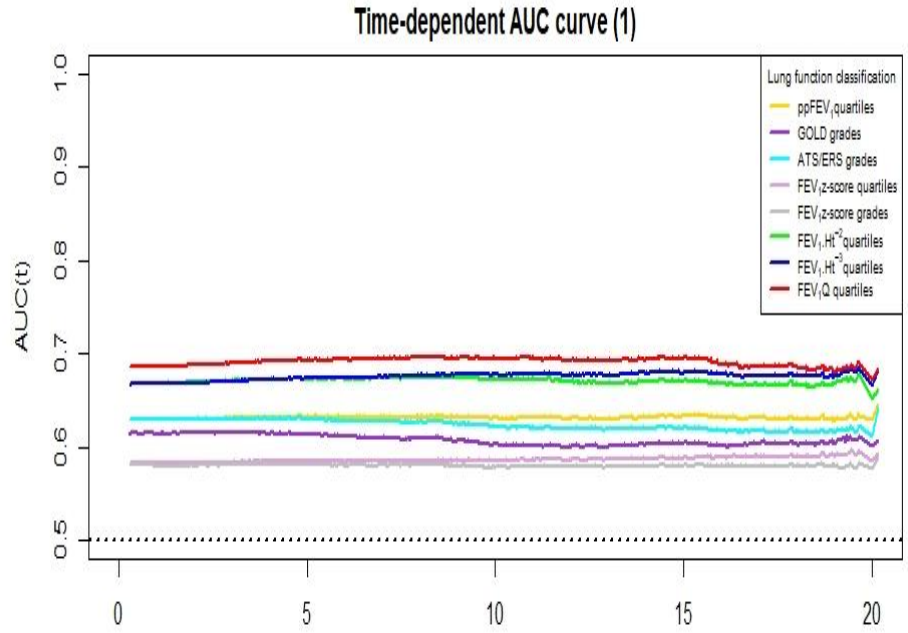


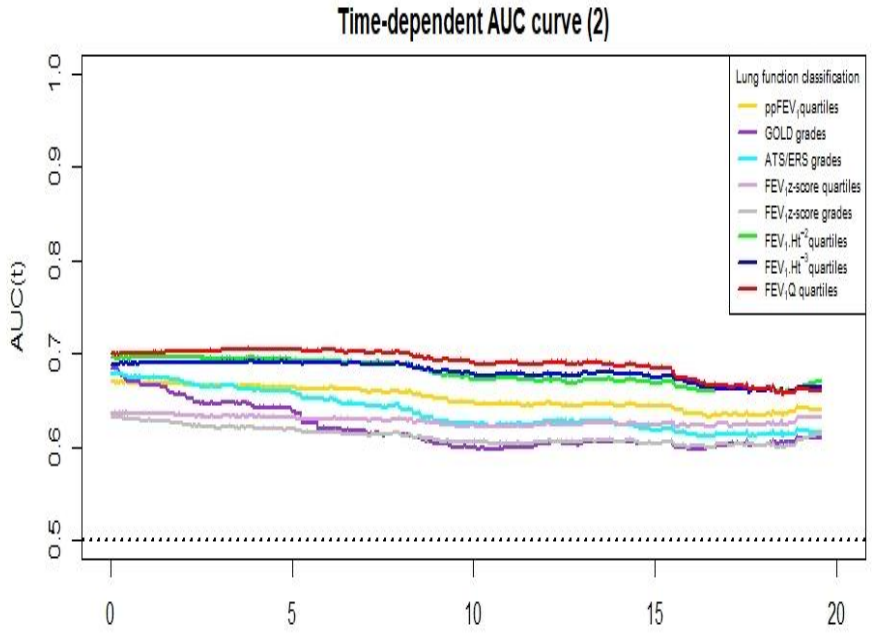


$ppFEV_1$	63.9	64.1	63.1	63.0	61.9
z-score	57.9	58.2	58.0	58.3	57.9
$FEV_1.Ht^{-2}$	68.0	68.5	67.9	68.0	66.8
$FEV_1.Ht^{-3}$	68.4	68.8	68.1	68.2	66.6
FEV_1Q	69.5	70.2	69.6	69.8	68.3

$ppFEV_1$	69.7	68.5	66.5	66.7	67.9
z-score	64.7	64.1	63.3	63.9	65.4
$FEV_1.Ht^{-2}$	71.8	71.4	70.4	70.9	71.3
$FEV_1.Ht^{-3}$	71.9	71.4	70.3	70.7	70.7
FEV_1Q	72.3	72.4	71.5	71.9	72.7

Figure 14. AUC curves for $ppFEV_1$, FEV_1 z-score, $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q for (1) all-cause mortality and (2) COPD hospitalization over the follow-up time (years) among people with COPD aged ≥40 years in the HUNT2 (1995-1997).





$ppFEV_1$ quartiles	62.9	63.2	63.1	63.3	63.3
GOLD grades	61.4	61.3	60.2	60.4	60.4
ATS/ERS grades	62.9	62.9	62.2	62.0	61.9
FEV_1 z-score quartiles	58.2	58.5	58.5	58.8	59.2
FEV_1 z-score grades	58.0	58.1	57.8	57.9	58.5
$FEV_1.Ht^{-2}$ quartiles	66.8	67.3	67.2	67.1	65.2
$FEV_1.Ht^{-3}$ quartiles	66.7	67.3	67.7	68.0	66.6
FEV_1Q quartiles	68.6	69.3	69.4	69.5	67.2

$ppFEV_1$ quartiles	66.9	66.3	64.7	64.4	65.7
GOLD grades	68.4	64.2	59.9	60.4	61.4
ATS/ERS grades	67.9	66.0	62.5	61.9	62.4
FEV_1 z-score quartiles	63.6	63.1	62.3	62.4	63.7
FEV_1 z-score grades	63.1	61.9	60.6	60.4	62.5
$FEV_1.Ht^{-2}$ quartiles	69.5	69.4	67.2	66.9	65.1
$FEV_1.Ht^{-3}$ quartiles	68.8	69.1	67.7	67.5	64.9
FEV_1Q quartiles	69.9	70.4	68.9	68.5	66.8

Figure 15. AUC curves for $ppFEV_1$ quartiles, GOLD grades, ATS/ERS grades, FEV_1 z-score quartiles, FEV_1 z-score grades, $FEV_1.Ht^{-2}$ quartiles, $FEV_1.Ht^{-3}$ quartiles, and FEV_1Q quartiles for (1) all-cause mortality and (2) COPD hospitalization over the follow-up time (years) among people with COPD aged ≥40 years in the HUNT2 (1995-1997).

5. Discussion

5.1 Summary of findings

The principle findings were:

1. Overall the prevalence of COPD decreased from HUNT2 (1995–1997) to HUNT3 (2006–2008). The prevalence of COPD decreased in men but in women it remained relatively stable [Paper I].
    - Consistently the prevalence of COPD was higher among men than women in both the HUNT2 and the HUNT3 [Paper I].
    - The cumulative incidence of COPD was 9.7% (men 11.9%, women 7.9%) over the 11-year period from HUNT2 to HUNT3 using the fixed-ratio criteria [Paper I].
    - The prevalence of respiratory symptoms seemed to increase from HUNT2 to HUNT3 [Paper I].
2. Mortality was better predicted by post-BD than by pre-BD lung function, however, they differed only by a small margin [Paper II].
    - The discrimination ability of pre-BD and post-BD lung function using GOLD grades among people with COPD was similar in predicting mortality [Paper II].
3. The GOLD 2007 classification was marginally better than the GOLD 2011 classification, where the GOLD 2017 classification was worst in predicting mortality and COPD hospitalization [Paper III].
4. FEV_1Q was the best predictor of mortality and COPD hospitalization compared to a broad range of commonly applied lung function measures such as $ppFEV_1$, FEV_1 z-score, $FEV_1.Ht^{-2}$, and $FEV_1.Ht^{-3}$ [Paper IV].

5.2 Methodological considerations

This thesis used observational study designs based on data from the HUNT (a population-based study). Hence, some methodological considerations must be considered for the interpretation of our findings.

5.2.1 Random error (lack of precision)

Random error causes a lack of precision of the estimates in a study. The measure of random error and procedures to limit the error are important. Random error is unexplained random variability in the data. The presence of random error usually reflects the fluctuation in the observed value from

the true value due to any factors that randomly affect the result of a measurement [155]. Random error may be due to the random variation in sampling, variable measurements, or variable occurrence of exposures, outcomes, and covariates [155]. Statistically, variance is a measure of random error, where statistically CI indicated the statistical precision. In this thesis, we have used 95% CI to present the precision of the estimates in all papers. The narrower CI, the higher the precision or the lower the random error [155].

Increasing the sample size improves the precision of estimates. In Papers I-IV, we have a good sample size (reported in section 3.3) to provide reasonable precision in the estimates. In Paper II, the estimates from the exposure variables with ≥4 categories have reduced precision due to the low number of people in a particular category of exposure of interest, which might be considered while interpreting the estimates.

5.2.2 Systematic error (lack of internal validity)

Systematic error causes a lack of internal validity of the estimates in a study. Systematic error cannot be limited by increasing the sample size [155]. Systematic error is an umbrella term that consists of different types of biases. Three main types of biases in studies exist: selection bias, information bias, and confounding [155].

5.2.2.1 Selection bias

Selection bias is defined as the erroneous selection of the sample for the study that does not represent the target population [156]. Selection bias is present when the association of exposure and outcome in the study sample is different from the association among those members of the target population who did not participate [155, 156]. Selection bias occurs when people do not participate in the study or do not respond to parts of data collection procedures, which is influenced by many factors such as lifestyle and attitude [156]. Selection bias mainly consists of non-response bias and loss to follow-up [155, 156].

This thesis included people aged ≥40 years from the HUNT2 and the HUNT3. The participation rate was reasonably high in the HUNT2 (75.2%) and the HUNT3 (61.6%). However, we cannot completely rule out the possibility of some selection bias. Studies have compared the participants and non-participants in the HUNT and they observed that lack of time and interest were main reasons for not participating [157, 158]. Additionally, only 4.7% women and 2.6% men reported illness as a reason for not participating [158]. We do not expect that selection bias might have a substantial impact to our estimates.

Additionally, we used a subgroup of samples from the HUNT Lung Study, where a 5% random sample was selected from the HUNT2 and 10% random sample were selected from the HUNT3, in addition to symptom samples drawn from both the HUNT studies. There was a high participation rate of 80% in the HUNT2 Lung Study and 73% in the HUNT3 Lung Study. Additionally, the distributions of age, sex, BMI, current smokers, and smoking pack-years were similar in participants and non-participants of the HUNT Lung Study. In Paper I, we weighted the estimates in our analysis to account for the sampling with unequal selection probabilities and loss to follow-up. We used the inverse probability of selection for the sample loss in the HUNT Lung Study and the predicted probability of response for the sample loss in the HUNT. In a sensitivity analysis, the weighted estimates were compared to estimates from the random sample in the HUNT Lung Study. We found close agreement of our weighted results not only with the random sample but also with the main questionnaire based on the entire participating population of the HUNT in terms of mean age, BMI, and smoking pack-years, and proportions of current smokers, asthma history, wheezing/dyspnoea, chronic bronchitis, cough phlegm, and cough daily. In Papers II, III, IV, we included the people with airflow limitation and/or COPD. We did not expect that our estimates were substantially altered by selection bias.

5.2.2.2 Information bias

Information bias is present when the information collected from the participants is subject to error [155, 156]. Measurement error or misclassification of participant information leads to information bias that may be differential or non-differential. Differential bias varies according to the value of other study variables including exposure and outcome. Differential bias may overestimate or underestimate the study results [155, 156]. Non-differential bias is unrelated to the value of other study variables, therefore usually bias results towards the null [155, 156].

We defined COPD based on lung function measurements. These measurements could be subject to measurement error, either by the participant's willingness or attitude to perform lung function measurement or by the procedures used to perform spirometry. During the lung function measurements, some people might not have fully exhaled which might have resulted in low estimated FVC. People performing spirometry with this measurement error may have falsely high FEV_1/FVC ratio, which would results in an underestimation of the prevalence of COPD [48]. We used two different guidelines for the measurements of lung function in the HUNT2 and HUNT3; namely the 1994 ATS-criteria [133] and 2005 ATS-ERS criteria [20] were used, respectively. Hence, this could lead to either underestimation or overestimation of the prevalence of COPD from HUNT2 to HUNT3. Furthermore, incorrect procedures facilitated by technicians could lead to non-

differential misclassification of the lung function measurements. However, for lung function measurements in the HUNT, trained technicians instructed the participants and performed the spirometry. The quality control methods applied for acceptability and reproducibility of spirometry were similar in the HUNT2 and the HUNT3, and the same 2-3 trained persons performed all evaluations. The method is described in detail in the methods section and elsewhere [30, 135]. Therefore, we do not expect that misclassification error from lung function measurements has materially affected our estimates. Furthermore, trained personnel collected all the HUNT study measurements such as BMI, systolic blood pressure, total cholesterol, and other physical measurements following a standard procedure that would reduce measurement errors. The HUNT data were also screened for extreme values that might indicate errors.

In the HUNT, the baseline information was collected through interview and self-administered questionnaire. There could be differential misclassification in the form of interviewer bias, recall bias, and reporting bias [155, 156]. Interviewer bias occurs when the interviewer/observer is aware of the study hypothesis, disease status, or exposure status [156]. Recall bias occurs when participants are influenced by their knowledge, attitude and perception on exposure and outcome status [155, 156]. Reporting bias occurs when participants over or under report the information that is in the direction they perceive are of interest to the researchers [156]. The HUNT was prospective in nature; therefore, this would minimize the occurrence of differential misclassification in the measurements of exposure due to the participant's disease or outcome status. Nevertheless, participants with respiratory symptoms were invited to the HUNT Lung Study and they were aware of medical doctor diagnosed COPD, which could have caused differential misclassification in reporting of the mMRC dyspnoea and exacerbation history (use of cortisone tablets). Hence, the ABCD groups that we defined using the information on mMRC dyspnoea and exacerbation might be subject to differential misclassification. Similarly, we could not completely rule out the possibilities of differential misclassification for asthma ever, chronic bronchitis, chronic cough, chronic phlegm, and dyspnoea/wheezing.

Additionally, hospitalization due to COPD could be misdiagnosed as asthma and vice versa. Due to the similarities in respiratory symptoms between COPD and asthma, we do expect some misclassification of hospitalization due to asthma. COPD is not common in early age, therefore to reduce the misclassification of hospitalization due to asthma, we have excluded people <40 years of age and defined our study sample of people with COPD as having airflow limitation and respiratory symptoms and/or self-reported doctor diagnosed COPD.

Furthermore, in this thesis, our main estimates were derived from crude models (Paper I: prevalence, Paper II, III, and IV: prediction) where we had complete information on the exposure

and outcomes. For the adjusted estimates, all the covariates had less than 10% missing except for physical activity that had 15% missing, which might have biased the estimates. However, the percentage of missing data was generally low and the corresponding effect on the results should be minimal. Furthermore, we have taken care of missing data by either performing multiple imputation (Paper I) or creating a missing indicator variable (missing information as unknown category) (Paper II, III, IV).

5.2.2.3 Confounding

Confounding occurs when an effect of an exposure is mixed with the effect of another variable [155]. Confounding could underestimate or overestimate the association between exposure and outcome. A variable is considered as confounder when it 1) is associated with the exposure but not affected by it and 2) is associated with the outcome or disease but not affected by it [155]. A confounder is a common cause of both the exposure and the outcome. A common example of a confounder is physical inactivity in the association between obesity and cardiovascular diseases, where physical inactivity is associated with both obesity and cardiovascular diseases. The estimated association between obesity and cardiovascular diseases is influenced by the effect of physical inactivity on both. To get the true effect of obesity on cardiovascular diseases, the confounder, physical inactivity should be taken into account. Randomization, restriction, stratification, standardization and statistical modelling can control for the bias due to confounding [155]. In addition to confounders mediators and colliders need to be considered [155]. A mediator is a variable that is on the casual path from exposure to outcome. A collider is a variable that is a common consequence of the exposure and the outcome [155]. Statistical adjustment of mediators and colliders could underestimate or overestimate the estimates.

In our studies, we used crude models (Model 1) for the majority of our main estimates. However, we also presented adjusted models (Model 2 and Model 3) in all the papers. Age and smoking are established risk factors for COPD [8]. The prevalence of COPD differed between the sexes in developed countries where men have a higher prevalence of COPD than women [70, 71]. Studies suggest that the women are more biologically susceptible to the effect of smoking on lungs than men are [71, 74-76]. We could have stratified the analyses among sexes, but due to the small sample size and to reserve the precision of estimates, we controlled for sex in the analysis. In addition to these variables, BMI and education are associated with COPD even after controlling for smoking pack-years [8]. Hence, we have controlled for BMI and education for the association of lung function with mortality and/or COPD hospitalization in Paper II, III, and IV. Additionally, we have controlled for physical activity and comorbidities in Model 3. Although it could be argued that

physical activity and comorbidities may be mediators or colliders, we do not expect that the adjusted estimates were materially biased, as the estimates were similar in all the models. However, we cannot completely rule out the possibility of residual confounding. Residual confounding may occur due to unknown confounders that were not controlled for. To have materially biased estimates the unknown confounder should have a strong association with the exposure and outcome and not be associated with any other known confounders that were controlled for in the model.

Most notably, in our papers II-IV, we primarily aimed to assess the prediction abilities of the various measures of lung function in predicting mortality and/or COPD hospitalization using crude models. Hence, confounding might not be an issue for these prognostic models.

5.2.3 Generalizability (external validity)

The external validity of a study is determined by its generalizability [155]. The generalizability is not only concerned with precision and internal validity of findings, but more with the representativeness of the findings to other populations [155]. Until 2018, Nord-Trøndelag was a County in central Norway, which had a homogenous (97% Caucasians) and a stable population. This former county was representative for the Norwegian population regarding age, income, morbidity, mortality, and other aspects [129]. Therefore, our study finding could be generalized to the Norwegian population and other European countries with similar ethnic majority. One should be cautious when generalizing the findings to multi-ethnic populations. We have included people aged ≥40 years; therefore, the findings could not be generalized to young adults.

Most notably, the prevalence of COPD and its trend can vary depending on the population studied. Therefore, our findings from Paper I may not be generalizable to other settings.

5.3 Appraisal of the principal findings

5.3.1 Prevalence and trend of COPD

In Paper I, we found that the prevalence of COPD decreased from HUNT2 (1995-1997) to HUNT3 (2006-2008), where it decreased among men but remained relatively stable in women. In both the HUNT2 and the HUNT3, the prevalence of COPD was higher among men compared to women. Intriguingly, the prevalence of respiratory symptoms increased from HUNT2 to HUNT3. The cumulative incidence of COPD was 9.7% over the 11-year period.

The prevalence of COPD in a population varies depending on diagnostic criteria and lung function measurement (pre-BD or post-BD). In our study, we have estimated the prevalence of COPD defined by the fixed-ratio criteria and LLN criteria in pre-BD spirometry. The estimated prevalence could be lowered by 20-40% using post-BD measurements as described by other studies

[28, 159, 160]. Additionally, the prevalence reported using the fixed-ratio criteria underestimates the prevalence of COPD in the younger population and overestimates in the older population [159, 160]. A comparable estimation of the prevalence of COPD in another population is often difficult to find, however most studies have used the fixed-ratio criteria to estimate the prevalence of COPD using either pre-BD or post-BD lung function measurements. Similar to our study, a meta-analysis based on pre-BD and post-BD from 64 European studies found 66.4 million people with COPD (13.7%) aged ≥30 years in 2010 [90]. Similarly, a study based on pre-BD in Canada estimated the prevalence of COPD to be 16.6% [92]. However, a Nordic country (Sweden) had lower estimates (11.2%) than our study [10], while estimates from western Norway (Bergen) in 2003-2005 (21%) were higher than our study [97]. The differences in these estimates might be due to different distribution of risk factors such as smoking and age of the population, time-period of the studies and age range of the study participants. For example, the proportion of current smokers was higher in the study from Bergen (30.0% vs. 17.0% in the HUNT3) [97]. Additionally, prescription records have shown that the prevalence of physician-diagnosed COPD varies geographically and is lower in central and western Norway compared to southern and eastern Norway [161]. The differences in physician-diagnosed COPD within different parts of Norway might related to health service utilization from patient and service provider perspectives as well.

We observed a decreased prevalence of COPD from 1995-1997 to 2006-2008. The trend of prevalence of COPD over time is closely related to the pattern of smoking and ageing [10, 93, 97, 162]. We observed a decreased in the proportion of current smokers in ours study, which is in line with the proportions from Norway i.e. 33% in 1995 to 24% in 2006. This might in part explain our observation of a decline prevalence of COPD [56]. However, in contrast to our study, the study in Bergen observed an increase in prevalence of COPD [97]. This might be due to 1) the age range of participants (40-99 years in the HUNT vs. 26-82 years and 35-90 years in the study from Bergen), 2) the time periods of the study (1995-1997 and 2006-2008 in the HUNT vs. 1996-1997 and 2003-2005), and 3) the prevalence of smoking (i.e. current smokers 28.6% and 17.0% in the HUNT vs. 33% and 30% in Bergen) and other risk factors [97]. While comparing our estimates to other populations or countries, two European studies from Spain and Sweden observed a similar decrease in the prevalence of COPD to ours [10, 94]. However, a recent meta-analysis reported that the prevalence of COPD increased in Europe from 11.8% in 1990 to 13.7% in 2010 [90]. Furthermore, no change in prevalence from 1978-1980 to 2000-2001 was found in a study from Finland [96].

In our study, we observed that men had a consistently higher prevalence of COPD than women. The difference in prevalence between sexes reduced at the later time point in HUNT3. The prevalence of COPD decreased in men and remained stable in women. The reduced difference over

the period could be explained by many factors. The proportion of current smokers was higher in women than men in 2006-2008 and a similar pattern was observed across Norway in 2006 [56]. Additionally, the mean number of smoking pack-years decreased in men but remained stable in women during this study. Furthermore, it has been argued that women are more physically susceptible to COPD from smoking compared to men [74]. The magnitude and direction of trend of COPD varies in men and women across the population studied [10, 93, 94, 96, 97]. Similar to our study, studies in Sweden, Finland and Spain observed the prevalence of COPD was consistently higher among men [10, 94, 96].

We observed that self-reported respiratory symptoms and asthma increased, however the trend could be affected by a changing clinical understanding of disease and current awareness of participants [163]. Our finding for asthma was consistent with a Swedish study [164]. However, they observed a decreased prevalence of other respiratory symptoms (longstanding cough, sputum production, chronic productive cough, and recurrent wheeze) [164]. The hospital admissions recorded in the Norwegian Patient Registry observed an increased prevalence of asthma over the years [165]. Asthma and respiratory symptoms are suggested as risk factors for COPD [8, 55, 80, 81]; hence, regardless of a decline in current smokers in our study, the increased prevalence of asthma and respiratory symptoms could in part explain the minimal decline in prevalence of COPD in our study.

The cumulative incidence of COPD in our study was higher than in Bergen (6.1% over a 9-year period) but lower than in Sweden (11.0% over a 7-year period) [166-168]. The 11-year cumulative incidence of 9.7% in our study could in part explain the minimal decline in prevalence of COPD. Updated estimates of the cumulative incidence of COPD are required.

5.3.2 Pre-BD and post-BD lung function in predicting mortality

In Paper II, decreasing pre-BD and post-BD lung function were associated with mortality. We observed that among people with airflow limitation, mortality was slightly better predicted by post-BD than by pre-BD lung function whether using $ppFEV_1$, FEV_1 z-score, FEV_1Q, or modified-GOLD categories. We observed similar results among people with COPD as well as using $ppFEV_1$, FEV_1 z-score, or FEV_1Q but pre-BD and post-BD similarly predicted mortality using GOLD grades.

Similar to our study, previous studies have found that decreased $ppFEV_1$, FEV_1 z-score, or FEV_1Q are associated with an increased risk of death [16, 115, 121, 169] and the risk of death increased with worsening GOLD-defined airflow limitation [170]. Among 5887 American individuals, Mannino et al. observed that a 10% increase in $ppFEV_1$ was associated with decreased

mortality by 13% for pre-BD and 16% for post-BD lung function [16]. Among 149,343 non-smokers from the UK, Gupta et al. observed that a decrease in 1-unit of FEV_1 z-score was associated with increased risk of death by 17% [169]. Among 26,967 European individuals from three cohorts, Miller et al. observed that worsening decile of FEV_1Q was associated with increased risk of death compared to the highest decile [121].

We directly compared the discrimination ability of pre-BD and post-BD lung function as a predictive marker (not adjusted for covariates) of mortality using a range of lung function measures/classification such as $ppFEV_1$, FEV_1 z-score, FEV_1Q, and modified-GOLD categories/GOLD grades, which makes our study the first study to investigate these measures. We used a crude model as in a clinical setting; a decision usually does not explicitly take other factors into account [52, 121]. We observed that post-BD was slightly better than pre-BD lung function to predict mortality, except for GOLD grades where pre-BD and post-BD similarly predicted mortality. Similar to our estimates at 6.5 years of follow-up, Fortis et al. [102] observed that post-BD was a stronger predictor for mortality than pre-BD lung function in models adjusted with covariates when followed for approximately 6.5 years. However, Mannino et .al. [16] found that pre-BD and post-BD lung function similarly predicted mortality at 20 years of follow-up. Compared to our study, when other predictors of mortality were included in models the results were similar to Mannino et al. at 20 years of follow-up [16]. This suggests that when other factors are considered, including post-BD lung function in models might not be more informative than pre-BD lung function at predicting long-term mortality. However, in respiratory medicine, there is no standard models used such as NORRISK2 [171], which is a Norwegian cardiovascular risk calculator based on Norwegian epidemiologic studies including the HUNT that is used in primary prevention of cardiovascular diseases, which includes age, sex, smoking, systolic blood pressure, total cholesterol, family history, hypertension, high-density lipoprotein (HDL) cholesterol. Similar to our study, Chen et al. [15] did not adjust for other factors when comparing pre-BD and post-BD lung function in predicting mortality using the GOLD grades, however in contrast to our finding, they observed that post-BD was better than pre-BD among people with COPD. The disagreement between Chen et al. [15] and our study might be due to methodological differences between studies (log-rank method vs. time-dependent AUC used in our study). The log-rank test [172] is commonly used to compare the survival curves of a model and the *p* value is calculated as a performance metric of the test. Reviewing two *p* values from two models might not be a sensitive approach to compare the performance of two models. Whereas we used a time-dependent AUC [151] method which provides AUC as a point estimate for a model that is then compared for the comparison of discrimination ability of two models.

Though GOLD recommends post-BD spirometry for the diagnosis and classification of COPD [55], often, only pre-BD lung function is used in clinical practice or in epidemiological studies. We observed that post-BD performs better than pre-BD lung function by a margin of approximately 2%. Hence, a clinical significance and cost effectiveness of this potential gain should be evaluated further. The finding that post-BD defined GOLD grades performed similarly to pre-BD among people with COPD could have clinical implications as to how procedures might be prioritised in different subgroups. Notably, the discrimination ability of pre-BD and post-BD lung function was generally poor except for FEV_1Q which had fair discrimination ability [173].

5.3.3 GOLD classifications of COPD in predicting mortality and COPD hospitalization

In Paper III, we found that the GOLD 2007 classification was marginally better than GOLD 2011, where the GOLD 2017 classification was the worst in predicting mortality and COPD hospitalization.

In our study, we observed that the three GOLD classifications distributed people with COPD into categories differentially and similar results have been observed by previous studies [13, 107, 174]. We observed that the number of people with the highest category in the GOLD 2017 classification (4.1% in groups C or D) was very low compared to the GOLD 2007 (13.9% in grades 3 or 4) and GOLD 2011 classification (16.8% in groups C or D). From groups C and D of the GOLD 2011 classification 78% of group C were moved to group A of the GOLD 2017 classification and 74% of group D people were moved to group B of the GOLD 2017 classification. In addition, we observed that when using the GOLD 2017 classification, 9% of group A people had severe COPD (GOLD grade 3) and 22% of group B people had severe or very severe COPD (GOLD grades 3 or 4). Although the recently updated GOLD 2019 report [165] recommended the use of the GOLD 2017 classification for prescribing an initial pharmacological treatment, the use of the GOLD 2017 classification to select a treatment approach should be cautioned for those in group A or B.

Although the GOLD classifications were meant to guide therapy, clinicians use it for risk classification at an individual level [52]. We observed that the worsening categories of the GOLD 2007 and GOLD 2011 classification were associated with mortality and COPD hospitalization. However, there was no clear pattern for the GOLD 2017 classification, where group D had lower hazards for mortality and COPD hospitalization than group C. Similar results to our study have been observed by other studies, where no clear pattern for mortality [13, 107, 174] and exacerbation [160] were observed across the categories of the GOLD 2017 classification. COPD hospitalization and exacerbation are related; however, not all exacerbations lead to hospitalizations. To our

knowledge, this is the first study to investigate the association between the GOLD 2017 classification and COPD hospitalization and compare its discrimination ability to the GOLD 2007 and GOLD 2011 classifications. We found that mortality and COPD hospitalization were best predicted by the GOLD 2007 classification, followed by the GOLD 2011 with a small margin of difference and least predicted by the GOLD 2017 classification over the 20-year follow-up. Similar to our study, a study by Lopez et al. [107] observed that the GOLD 2011 classification predicted mortality better than the GOLD 2017 classification. In contrast to our study, Gedebjerg et al. [13] found that the three GOLD classifications did not differ significantly in predicting respiratory and all-cause mortality. Similarly, three studies [109, 160, 175] have observed that the GOLD 2017 and the GOLD 2011 classifications predicted exacerbation similarly well. Furthermore, when the GOLD 2017 classification was divided into a 16 sub-group classification by severity of airflow limitation, Gedebjerg et al. found that the 16 sub-group classification predicted mortality slightly better than the GOLD classification [13]. Similar results were observed by Le et al. [176] to predict mortality, respiratory mortality, hospitalization, and respiratory hospitalization when 16 sub-group classification was compared to the GOLD 2011 and the GOLD 2017 classifications. We attempted to repeat this analysis but we had sparse data for this classification with no observations in some sub-groups and highly imprecise estimates.

Although, in our study, the GOLD 2007 classification was a better predictor, all classifications were generally poor prognostic markers for mortality and COPD hospitalization [173]. The best prognostic marker might not necessarily be the best guide to pharmaceutical treatment because two individuals might have the same risk of mortality for different reasons, which would indicate different treatment strategies; therefore, development in this area is warranted. Classifications based on other lung function measures or additional criteria such as symptoms, exacerbations, and biomarkers should be suggested to assess prognosis.

5.3.4 Spirometric classifications of COPD in predicting mortality and COPD hospitalization

In Paper IV, we found that among all lung function measures, FEV_1Q was the best predictor of mortality and COPD hospitalization, followed by $FEV_1.Ht^{-2}$ and $FEV_1.Ht^{-3}$ at 20 years and over the follow-up time.

Firstly, in our study, we observed that with the lower quartiles of the $ppFEV_1$, FEV_1 z-score, $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q lung function measures, the risk of death and COPD hospitalization increased. Others have observed similar results for mortality [14, 113, 114, 121, 123-125], exacerbation [113], and all-cause hospitalization [123, 125]. Among 793 people (40% people with COPD), Pedone et al. [114] observed similar results, where the adjusted HR for

mortality of the lowest 5th quintile was 4.45 for FEV_1Q and 3.28 for $ppFEV_1$ compared to the highest quantile. Until now, no studies have investigated the risk of COPD hospitalization. Similar results to our study have been observed for exacerbation, where among 296 people with COPD, Huang et al. [113] reported adjusted ORs of 4.03 and 3.02 for the lowest 4th quartile of FEV_1Q and $ppFEV_1$, respectively.

Lung function measures such as $ppFEV_1$ and FEV_1 z-score are based on reference values predicted by reference equations but $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q lung function measures are independent of reference equations [121]. The measurement $ppFEV_1$, one of the most widely used, has been criticized due to its susceptibility to physiological variation and poor prediction ability [14, 111-113]. The measurement FEV_1 z-score was recommended, which avoids bias due to physiological variation [111, 112]. Vaz Fragoso et al. [111] used the reference equation from NHANES III [117] and found that severe COPD based on FEV_1 z-score was associated with high risk of death and respiratory symptoms. Tejero et al. [115] observed that mortality was predicted worse by FEV_1 z-score compared to $ppFEV_1$ using GLI reference equations [24]. Studies have observed that the GLI reference equation better describes a healthy population than the ECSC reference equation [24, 30, 119], therefore the performance of reference dependent lung function measures may also vary with reference equations used [24, 30, 34, 118]. Growing evidence suggests reference independent lung function measures for the classification of COPD severity. Pioneering work by Miller et al. [14, 121, 124] found that the reference independent lung function measures such as $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q correlate with mortality better than those that depend on reference equations, where FEV_1Q was the best predictor [121]. Our finding corresponds to the finding by Miller et al. [121] and many others [113, 114, 125], where we extends this knowledge by investigating the discrimination ability for COPD hospitalization.

The measurements $ppFEV_1$ and FEV_1 z-score are based on reference values and largely depend on the choice of reference equation [55, 111, 112]. Accordingly, the performance of the methods of classification of COPD severity based on these lung function measures might vary with reference values. In a clinical setting, information on age, sex, and height of COPD patients is easily available. Therefore, using FEV_1Q (or other measures that are independent of reference equations) for risk classification of COPD patients might be easy to apply and avoid variation due to dependence on reference equations [121]. The choice of the lower limit of survival among sexes for the calculation of FEV_1Q could be argued and further investigated. In this study, we used 0.5L for men and 0.4L for women as a lower limit of survival as suggested by Miller et al., which were generated using a large population (3 cohorts) of 26,967 individuals (people with COPD and healthy people) from Europe [121].

The classification of COPD severity has been clinically useful for guiding therapy and is used for risk classification at individual level [52, 55]. The discrimination ability of a lung function measure for the classification of COPD severity largely depends on the choices of cut-offs. For example, the GOLD grades, ATS/ERS grades, and ppFEV_1 quartiles had different discrimination abilities in our study. Huang et al [113] observed similar results. Therefore, widely acceptable optimal cut-offs of $FEV_1.Ht^{-2}$, $FEV_1.Ht^{-3}$, and FEV_1Q that represents the classification of COPD severity should be investigated further. Furthermore, reference independent lung function measures in combination with symptoms, exacerbations, and/or biomarkers should be investigated further.

6. Conclusions

We found that the prevalence of COPD decreased from HUNT2 (1995-1997) to HUNT3 (2006-2008). The prevalence of COPD was consistently higher among men than among women in both the HUNT2 and the HUNT3, where the prevalence of COPD decreased among men but remained relatively stable among women. Intriguingly, the prevalence of respiratory symptoms increased from HUNT2 to HUNT3. The cumulative incidence of COPD was 9.7% over an 11-year period.

We found that post-BD lung function was marginally better than pre-BD lung function as a predictive marker of mortality. However, among people with COPD, pre-BD and post-BD lung function similarly predicted mortality using GOLD grades. The clinical significance and cost effectiveness of the potential gain in discrimination ability of post-BD lung function compared to pre-BD should be evaluated further.

Our study observed that the GOLD 2007 classification was marginally better than GOLD 2011 classification, where the GOLD 2017 classification was worst in predicting mortality and COPD hospitalization. This implies that the classification of COPD based on symptom and exacerbation is less informative for risk classification at an individual level and does not compensate for lung function.

We found that among a broad range of lung function measures, FEV_1Q was the best predictor of mortality and COPD hospitalization, followed by $FEV_1.Ht^{-2}$ and $FEV_1.Ht^{-3}$. This suggests that the reference independent lung function measures might performed better than lung function measures ($ppFEV_1$ and FEV_1 z-score) that depend on reference equation. A widely acceptable cut-offs of FEV_1Q that represents the classification of COPD severity should be investigated further.

Overall, this thesis highlights that the prevalence of COPD has decreased. The continual decrease in prevalence of COPD could be expected, which might be reflected by the continual decrease in the smoking behaviours that is now mostly observed in developed countries. To the current knowledge, this thesis adds valuable information on the prediction abilities of different lung function measures or classifications of COPD and supports the development of the classification of COPD in to areas such as reference independent lung function measures.

References

1. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary diesease, 2017. [Accessed 01 August 2017] Available from URL: http://goldcopd.org/.*
2. The economic burden of lung disease. 2017 [cited 2017 August 01]; Available from: http://www.erswhitebook.org/chapters/the-economic-burden-of-lung-disease/.
3. World Health Organization. *The top 10 causes of death. 2016. [Updated 24 May 2018] [Accessed 01 June 2019] Available from URL: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.*
4. Naghavi, M., et al., *Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016.* The Lancet, 2017. **390**(10100): p. 1151-1210.
5. World Health Organization: *Chronic obstructive pulmonary disease (COPD). 2016, http://www.who.int/mediacentre/factsheets/fs315/en/, Accessed 01 Aug 2017.*
6. Norwegian Institute of Public Health. *Chronic Obstructive Pulmonary Disease (COPD) in Norway. [Updated 21 February 2018] [Accessed 01 June 2019] Available from URL: https://www.fhi.no/en/op/hin/health-disease/copd/.*
7. Nielsen, R., et al., *Present and future costs of COPD in Iceland and Norway: results from the BOLD study.* Eur Respir J, 2009. **34**(4): p. 850-7.
8. Hooper, R., et al., *Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project.* European Respiratory Journal, 2012. **39**(6): p. 1343.
9. Northern Norway Regional Health Authority: *Centre for Clinical Documentation and Evaluation (SKDE). COPD Healthcare Atlas, 2018. [Accessed 10 March 2019] Available from URL: https://helseatlas.no/sites/default/files/copd-healthcare-atlas.pdf.*
10. Backman, H., et al., *Decreased prevalence of moderate to severe COPD over 15 years in northern Sweden.* Respir Med, 2016. **114**: p. 103-10.
11. López-Campos, J.L., W. Tan, and J.B. Soriano, *Global burden of COPD.* Respirology, 2016. **21**(1): p. 14-23.
12. Riley, C.M. and F.C. Sciurba, *Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease: A ReviewDiagnosis and Outpatient Management of Chronic Obstructive Pulmonary DiseaseDiagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease.* JAMA, 2019. **321**(8): p. 786-797.
13. Gedebjerg, A., et al., *Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study.* Lancet Respir Med, 2018. **6**(3): p. 204-212.
14. Miller, M.R., O.F. Pedersen, and A. Dirksen, *A new staging strategy for chronic obstructive pulmonary disease.* Int J Chron Obstruct Pulmon Dis, 2007. **2**(4): p. 657-63.
15. Chen, C.Z., et al., *Using post-bronchodilator FEV(1) is better than pre-bronchodilator FEV(1) in evaluation of COPD severity.* Copd, 2012. **9**(3): p. 276-80.
16. Mannino, D.M., E. Diaz-Guzman, and S. Buist, *Pre- and post-bronchodilator lung function as predictors of mortality in the Lung Health Study.* Respiratory Research, 2011. **12**(1): p. 136-136.
17. Rabe, K.F. and H. Watz, *Chronic obstructive pulmonary disease.* The Lancet, 2017. **389**(10082): p. 1931-1940.
18. Rennard, S.I. and M.B. Drummond, *Early chronic obstructive pulmonary disease: definition, assessment, and prevention.* Lancet (London, England), 2015. **385**(9979): p. 1778-1788.
19. Barnes, P.J., *Chronic Obstructive Pulmonary Disease.* New England Journal of Medicine, 2000. **343**(4): p. 269-280.
20. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-38.

21. Molnar, C. and Gair, J., *Concepts of Biology-1st Canadian Edition (Open text book).* 2012; *Available from: https://opentextbc.ca/biology/figure_39_03_05f/.*
22. Pulsenotes. *Lung function tests.* [Accessed 01 January 2019] *Available from URL: https://app.pulsenotes.com/medicine/respiratory/notes/lung-function-tests.*
23. Pellegrino, R., et al., *Interpretative strategies for lung function tests.* Eur Respir J, 2005. **26**(5): p. 948-68.
24. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values.* The European respiratory journal, 2012. **40**(6): p. 1324-1343.
25. National Institute for Health and Care Excellence. *Chronic obstructive pulmonary disease in over 16s: diagnosis and management*, 2018. [Accessed 01 January 2019] *Available from URL: https://www.nice.org.uk/guidance/ng115.*
26. Wollmer, P. and G. Engström, *Fixed ratio or lower limit of normal as cut-off value for FEV1/VC: An outcome study.* Respiratory Medicine, 2013. **107**(9): p. 1460-1462.
27. Agusti, A. and R. Faner, *Lung function trajectories in health and disease.* The Lancet Respiratory Medicine.
28. Johannessen, A., et al., *Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study.* Thorax, 2005. **60**(10): p. 842-7.
29. Johannessen, A., et al., *Post-bronchodilator spirometry reference values in adults and implications for disease management.* Am J Respir Crit Care Med, 2006. **173**(12): p. 1316-25.
30. Langhammer, A., et al., *Global Lung Function Initiative 2012 reference equations for spirometry in the Norwegian population.* Eur Respir J, 2016. **48**(6): p. 1602-1611.
31. Backman, H., et al., *The global Lund function initiative (GLI) reference values do not reflect lung function in the Nordic countries.* European Respiratory Journal, 2015. **46**(suppl 59): p. PA5064.
32. Kirkby, J., et al., *Global lung function initiative (GLI) spirometry equations: Comparison of lung function between indigenous Indian and UK-Indian children.* European Respiratory Journal, 2013. **42**(Suppl 57): p. P1224.
33. Hankinson, J.L., et al., *Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study.* Chest, 2010. **137**(1): p. 138-145.
34. Moreira, S., et al., *Comparison of the FEV1 value from five reference equations: ESCS 71|83|93, NHANES and GLI.* European Respiratory Journal, 2017. **50**(suppl 61): p. PA2507.
35. Cooper, B.G., et al., *The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together.* Breathe (Sheffield, England), 2017. **13**(3): p. e56-e64.
36. Kainu, A., et al., *Reference values of spirometry for Finnish adults.* Clinical Physiology and Functional Imaging, 2016. **36**(5): p. 346-358.
37. *Backman, H. Lung function and prevalence trends in asthma and COPD: The obstructive lung disease in northern Sweden (Doctoral thesis XVI). 2016. Umeå University, Umeå, Sweden. .*
38. Vestbo, J., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary.* Am J Respir Crit Care Med, 2013. **187**(4): p. 347-65.
39. Kessler, R., et al., *Symptom variability in patients with severe COPD: a pan-European cross-sectional study.* Eur Respir J, 2011. **37**(2): p. 264-72.
40. Miravitlles, M. and A. Ribera, *Understanding the impact of symptoms on the burden of COPD.* Respiratory Research, 2017. **18**(1): p. 67.

41. Huang, W.-C., et al., *Wheezing, a significant clinical phenotype of COPD: experience from the Taiwan Obstructive Lung Disease Study.* International journal of chronic obstructive pulmonary disease, 2015. **10**: p. 2121-2126.
42. *Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society.* Am J Respir Crit Care Med, 1999. **159**(1): p. 321-40.
43. Çolak, Y., et al., *Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry.* European Respiratory Journal, 2019: p. 1900734.
44. Burge, S. and J.A. Wedzicha, *COPD exacerbations: definitions and classifications.* European Respiratory Journal, 2003. **21**(41 suppl): p. 46s.
45. Vogelmeier, C.F., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary.* Am J Respir Crit Care Med, 2017. **195**(5): p. 557-582.
46. Donaldson, G.C., et al., *Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease.* Thorax, 2002. **57**(10): p. 847-52.
47. Halpin, D.M., et al., *Exacerbation frequency and course of COPD.* Int J Chron Obstruct Pulmon Dis, 2012. **7**: p. 653-61.
48. *Leivseth, L. Chronic obstructive pulmonary disease; lung function, respiratroy symptoms, and mortality (Doctoral thesis). 2013. Norwegian University of Science and Technology NTNU, Trondheim, Norway. .*
49. Montserrat-Capdevila, J., et al., *Risk of exacerbation in chronic obstructive pulmonary disease: a primary care retrospective cohort study.* BMC family practice, 2015. **16**: p. 173-173.
50. Hoogendoorn, M., et al., *Association between lung function and exacerbation frequency in patients with COPD.* Int J Chron Obstruct Pulmon Dis, 2010. **5**: p. 435-44.
51. Lange, P., et al., *Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease.* New England Journal of Medicine, 2015. **373**(2): p. 111-122.
52. Soriano, J.B., et al., *Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data.* Lancet Respir Med, 2015. **3**(6): p. 443-50.
53. Vasquez, M.M., et al., *Low Lung Function in Young Adult Life Is Associated with Early Mortality.* American Journal of Respiratory and Critical Care Medicine, 2017. **195**(10): p. 1399-1401.
54. Soriano, J.B., et al., *Patterns of comorbidities in newly diagnosed COPD and asthma in primary care.* Chest, 2005. **128**(4): p. 2099-107.
55. Barnes, P.J. and B.R. Celli, *Systemic manifestations and comorbidities of COPD.* Eur Respir J, 2009. **33**(5): p. 1165-85.
56. Lindberg, A., et al., *Co-morbidity in mild-to-moderate COPD: comparison to normal and restrictive lung function.* Copd, 2011. **8**(6): p. 421-8.
57. Vestbo, J., S.S. Hurd, and R. Rodriguez-Roisin, *The 2011 revision of the global strategy for the diagnosis, management and prevention of COPD (GOLD) – why and what?* The Clinical Respiratory Journal, 2012. **6**(4): p. 208-214.
58. Silverman, E.K. and F.E. Speizer, *Risk factors for the development of chronic obstructive pulmonary disease.* Med Clin North Am, 1996. **80**(3): p. 501-22.
59. Johannessen, A., et al., *Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults.* Respirology, 2012. **17**(3): p. 499-505.
60. Trupin, L., et al., *The occupational burden of chronic obstructive pulmonary disease.* Eur Respir J, 2003. **22**(3): p. 462-9.
61. Diette, G.B., et al., O*bstructive lung disease and exposure to burning biomass fuel in the indoor environment.* Global heart, 2012. **7**(3): p. 265-270.

62. Abbey, D.E., et al., *Long-term particulate and other air pollutants and lung function in nonsmokers.* Am J Respir Crit Care Med, 1998. **158**(1): p. 289-98.
63. Soriano, J.B. and R. Rodríguez-Roisin, *Chronic Obstructive Pulmonary Disease Overview.* Proceedings of the American Thoracic Society, 2011. **8**(4): p. 363-367.
64. Stoller, J.K. and L.S. Aboussouan, *Alpha1-antitrypsin deficiency.* Lancet, 2005. **365**(9478): p. 2225-36.
65. Hunninghake, G.M., et al., *MMP12, Lung Function, and COPD in High-Risk Populations.* New England Journal of Medicine, 2009. **361**(27): p. 2599-2608.
66. McCloskey, S.C., et al., *Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction.* Am J Respir Crit Care Med, 2001. **164**(8 Pt 1): p. 1419-24.
67. Akgün, K.M., K. Crothers, and M. Pisani, *Epidemiology and management of common pulmonary diseases in older persons.* The journals of gerontology. Series A, Biological sciences and medical sciences, 2012. **67**(3): p. 276-291.
68. Mannino, D.M. and A.S. Buist, *Global burden of COPD: risk factors, prevalence, and future trends.* The Lancet, 2007. **370**(9589): p. 765-773.
69. Buist, A.S., et al., *International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study.* Lancet, 2007. **370**(9589): p. 741-50.
70. Landis, S.H., et al., *Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 597-611.
71. Barnes, P.J., *Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms.* American Journal of Respiratory and Critical Care Medicine, 2016. **193**(8): p. 813-814.
72. Statistics Norway. *Smoking habits.* http://www.ssb.no/en/royk, updated 20 Jan 2017 (accessed 02 Aug 2017).
73. Soriano, J.B., et al., *Recent trends in physician diagnosed COPD in women and men in the UK.* Thorax, 2000. **55**(9): p. 789.
74. Sorheim, I.C., et al., *Gender differences in COPD: are women more susceptible to smoking effects than men?* Thorax, 2010. **65**(6): p. 480-5.
75. Langhammer, A., et al., *Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT).* J Epidemiol Community Health, 2000. **54**(12): p. 917-22.
76. Langhammer, A., et al., *Sex differences in lung vulnerability to tobacco smoking.* Eur Respir J, 2003. **21**(6): p. 1017-23.
77. Barker, D.J., et al., *Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease.* BMJ (Clinical research ed.), 1991. **303**(6804): p. 671-675.
78. Todisco, T., et al., *Mild prematurity and respiratory functions.* Eur J Pediatr, 1993. **152**(1): p. 55-8.
79. Lawlor, D.A., S. Ebrahim, and G. Davey Smith, *Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis.* Thorax, 2005. **60**(10): p. 851-8.
80. Bui, D.S., et al., *Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life.* The Lancet Respiratory Medicine, 2018. **6**(7): p. 535-544.
81. Martinez, F.D., *Early-Life Origins of Chronic Obstructive Pulmonary Disease.* New England Journal of Medicine, 2016. **375**(9): p. 871-878.
82. Beran, D., et al., *Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries.* Lancet Respir Med, 2015. **3**(2): p. 159-170.

83. Prescott, E., P. Lange, and J. Vestbo, *Socioeconomic status, lung function and admission to hospital for COPD: results from the Copenhagen City Heart Study.* Eur Respir J, 1999. **13**(5): p. 1109-14.
84. Sedgwick, P., *Prevalence and incidence.* BMJ, 2010. **341**: p. c4709.
85. Rycroft, C.E., et al., *Epidemiology of chronic obstructive pulmonary disease: a literature review.* Int J Chron Obstruct Pulmon Dis, 2012. **7**: p. 457-94.
86. Atsou, K., C. Chouaid, and G. Hejblum, *Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review.* BMC Med, 2011. **9**: p. 7.
87. Halbert, R.J., et al., *Global burden of COPD: systematic review and meta-analysis.* Eur Respir J, 2006. **28**(3): p. 523-32.
88. Hvidsten, S.C., et al., *Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population.* Clin Respir J, 2010. **4**(1): p. 13-21.
89. Lindstrom, M., et al., *Underdiagnosis of chronic obstructive pulmonary disease in Northern Sweden.* Int J Tuberc Lung Dis, 2002. **6**(1): p. 76-84.
90. Adeloye, D., et al., *Global and regional estimates of COPD prevalence: Systematic review and meta-analysis.* J Glob Health, 2015. **5**(2): p. 020415.
91. Danielsson, P., et al., *The prevalence of chronic obstructive pulmonary disease in Uppsala, Sweden--the Burden of Obstructive Lung Disease (BOLD) study: cross-sectional population-based study.* Clin Respir J, 2012. **6**(2): p. 120-7.
92. Evans, J., et al., *Estimating the prevalence of COPD in Canada: Reported diagnosis versus measured airflow obstruction.* Health Rep, 2014. **25**(3): p. 3-11.
93. Ford, E.S., et al., *Trends in the Prevalence of Obstructive and Restrictive Lung Function Among Adults in the United States: Findings From the National Health and Nutrition Examination Surveys From 1988-1994 to 2007-2010.* Chest, 2013. **143**(5): p. 1395-1406.
94. Soriano, J.B., et al., *Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997-2007.* Eur Respir J, 2010. **36**(4): p. 758-65.
95. Tilert, T., et al., *Estimating the U.S. prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007-2010.* Respir Res, 2013. **14**: p. 103.
96. Vasankari, T.M., et al., *No increase in the prevalence of COPD in two decades.* Eur Respir J, 2010. **36**(4): p. 766-73.
97. Waatevik, M., et al., *Increased prevalence of chronic obstructive pulmonary disease in a general population.* Respir Med, 2013. **107**(7): p. 1037-45.
98. Hansen, J.G., et al., *The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study.* Copd, 2008. **5**(6): p. 347-52.
99. Sterk, P.J., *Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1.* Eur Respir J, 2004. **23**(4): p. 497-8.
100. Fromer, L., *Diagnosing and treating COPD: understanding the challenges and finding solutions.* International Journal of General Medicine, 2011. **4**: p. 729-739.
101. Yawn, B.P. and P.C. Wollan, *Knowledge and attitudes of family physicians coming to COPD continuing medical education.* International Journal of Chronic Obstructive Pulmonary Disease, 2008. **3**(2): p. 311-318.
102. Fortis, S., et al., *Predictive value of prebronchodilator and postbronchodilator spirometry for COPD features and outcomes.* BMJ Open Respiratory Research, 2017. **4**(1).
103. Johannessen, A., et al., *Comparison of 2011 and 2007 Global Initiative for Chronic Obstructive Lung Disease guidelines for predicting mortality and hospitalization.* Am J Respir Crit Care Med, 2013. **188**(1): p. 51-9.
104. Lange, P., et al., *Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population.* Am J Respir Crit Care Med, 2012. **186**(10): p. 975-81.

105. Chen, C.Z., et al., *Validation of the GOLD 2013 classification in predicting exacerbations and mortality in Taiwanese patients with chronic obstructive pulmonary disease.* J Formos Med Assoc, 2015. **114**(12): p. 1258-66.
106. Leivseth, L., et al., *GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway.* Thorax, 2013. **68**(10): p. 914.
107. Cabrera Lopez, C., et al., *Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes.* Am J Respir Crit Care Med, 2018. **197**(4): p. 463-469.
108. Criner, R.N., et al. *Mortality and exacerbations by Global Initiative for Chronic Obstructive Lung Disease Groups ABCD: 2011 versus 2017 in the COPDGene® Cohort.* Chronic Obstr Pulm Dis, 2019. 6(1): 64-73. *doi: http://doi.org/10.15326/jcopdf.6.1.2018.0130.*
109. Han, M.-Z., et al., *Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients.* International journal of chronic obstructive pulmonary disease, 2018. **13**: p. 3425-3433.
110. *Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary diesease, 2019. [Accessed 02 February 2019] Available from URL: http://goldcopd.org/.*
111. Fragoso, C.A., et al., *Staging the severity of chronic obstructive pulmonary disease in older persons based on spirometric Z-scores.* J Am Geriatr Soc, 2011. **59**(10): p. 1847-54.
112. Quanjer, P.H., et al., *Grading the severity of airways obstruction: new wine in new bottles.* European Respiratory Journal, 2014. **43**(2): p. 505.
113. Huang, T.H., et al., *Comparison of different staging methods for COPD in predicting outcomes.* Eur Respir J, 2018. **51**(3).
114. Pedone, C., et al., *Alternative ways of expressing FEV1 and mortality in elderly people with and without COPD.* European Respiratory Journal, 2013. **41**(4): p. 800.
115. Tejero, E., et al., *Classification of Airflow Limitation Based on z-Score Underestimates Mortality in Patients with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2017. **196**(3): p. 298-305.
116. Oh, D.K., et al., *Comparison of the fixed ratio and the Z-score of FEV(1)/FVC in the elderly population: a long-term mortality analysis from the Third National Health and Nutritional Examination Survey.* International journal of chronic obstructive pulmonary disease, 2018. **13**: p. 903-915.
117. Hankinson, J.L., J.R. Odencrantz, and K.B. Fedan, *Spirometric reference values from a sample of the general U.S. population.* Am J Respir Crit Care Med, 1999. **159**(1): p. 179-87.
118. Langhammer, A., et al., *Forced spirometry reference values for Norwegian adults: the Bronchial Obstruction in Nord-Trondelag Study.* Eur Respir J, 2001. **18**(5): p. 770-9.
119. Hulo, S., et al., *Global Lung Function Initiative reference equations better describe a middle-aged, healthy French population than the European Community for Steel and Coal values.* European Respiratory Journal, 2016. **48**(6): p. 1779.
120. Sorlie, P.D., W.B. Kannel, and G. O'Connor, *Mortality associated with respiratory function and symptoms in advanced age. The Framingham Study.* Am Rev Respir Dis, 1989. **140**(2): p. 379-84.
121. Miller, M.R. and O.F. Pedersen, *New concepts for expressing forced expiratory volume in 1 s arising from survival analysis.* Eur Respir J, 2010. **35**(4): p. 873-82.
122. Fletcher, C., et al., *The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London*. 1976: Oxford University Press, 37 Dover Street, London. W1X 4AH. xix + 272 pp.
123. Turkeshi, E., et al., *Short-term prognostic value of forced expiratory volume in 1 second divided by height cubed in a prospective cohort of people 80 years and older.* BMC geriatrics, 2015. **15**: p. 15-15.

124. Miller, M.R., et al., *Improved survival prediction from lung function data in a large population sample.* Respiratory Medicine, 2009. **103**(3): p. 442-448.
125. Hegendorfer, E., et al., *Predictive Value of Different Expressions of Forced Expiratory Volume in 1 Second (FEV1) for Adverse Outcomes in a Cohort of Adults Aged 80 and Older.* J Am Med Dir Assoc, 2017. **18**(2): p. 123-130.
126. Vaz Fragoso, C.A., et al., *Staging the Severity of Chronic Obstructive Pulmonary Disease in Older Persons Based on Spirometric z-Scores.* Journal of the American Geriatrics Society, 2011. **59**(10): p. 1847-1854.
127. Mann, C.J., *Observational research methods. Research design II: cohort, cross sectional, and case-control studies.* Emergency Medicine Journal, 2003. **20**(1): p. 54.
128. Talseth, A., et al., *Risk factors for requiring cholecystectomy for gallstone disease in a prospective population-based cohort study: Risk factors for cholecystectomy in gallstone disease*. Vol. 103. 2016.
129. Holmen J, et al., *The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation.* Norsk Epidemiologi, 2003. **13**(1): p. 19-32.
130. Krokstad, S., et al., *Cohort Profile: the HUNT Study, Norway.* Int J Epidemiol, 2013. **42**(4): p. 968-77.
131. Holmen, T.L., et al., *Cohort profile of the Young-HUNT Study, Norway: a population-based study of adolescents.* Int J Epidemiol, 2014. **43**(2): p. 536-44.
132. Quanjer, P.H., et al., *Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society.* Eur Respir J Suppl, 1993. **16**: p. 5-40.
133. *Standardization of Spirometry, 1994 Update. American Thoracic Society.* Am J Respir Crit Care Med, 1995. **152**(3): p. 1107-36.
134. *Langhammer, A. Respiratory symptoms. lung function, and bone mineral density in a comprehensive population survey: The Nord-Trøndelag Health Study 1995-97 (Doctoral thesis). 2003. NTNU, Trondheim.* .
135. Hankinson, J.L., et al., *Use of forced vital capacity and forced expiratory volume in 1 second quality criteria for determining a valid test.* Eur Respir J, 2015. **45**(5): p. 1283-92.
136. Stanojevic, S., et al., *Reference ranges for spirometry across all ages: a new approach.* American journal of respiratory and critical care medicine, 2008. **177**(3): p. 253-260.
137. Wan, E.S., et al., *Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene.* Respiratory research, 2014. **15**(1): p. 89-89.
138. Mahler, D.A. and C.K. Wells, *Evaluation of clinical methods for rating dyspnea.* Chest, 1988. **93**(3): p. 580-6.
139. Brogger, J.C., P.S. Bakke, and A. Gulsvik, *Comparison of respiratory symptoms questionnaires.* Int J Tuberc Lung Dis, 2000. **4**(1): p. 83-90.
140. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-586.
141. Pedersen, A.G. and C.L. Ellingsen, *Data quality in the Causes of Death Registry.* Tidsskr Nor Laegeforen, 2015. **135**(8): p. 768-70.
142. *Norwegian Institute of Public Health. Cause of Death Statistics. https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/cause-of-death-registry-/, updated 18 April 2019 (accessed 05 June 2019).*
143. *Helse Nord-Trøndelag. https://hnt.no/helsefaglig/forskning/forskningsstotte/utlevering-av-forskningsdata, updated 04 June 2019 (accessed 24 June 2019).*
144. Grambsch, P.M. and T.M. Therneau, *Proportional Hazards Tests and Diagnostics Based on Weighted Residuals.* Biometrika, 1994. **81**(3): p. 515-526.
145. Belsley, D.A., E. Kuh, and R.E. Welsch, *Regression diagnostics : identifying influential data and sources of collinearity*. 1980: New York (N.Y.) : Wiley.

146. O'Brien, R.M., *A Caution Regarding Rules of Thumb for Variance Inflation Factors.* Quality & Quantity, 2007. **41**(5): p. 673-690.
147. Bozdogan, H., *Model selection and Akaike's Information Criterion (AIC): The general theory and its analytical extensions.* Psychometrika, 1987. **52**(3): p. 345-370.
148. May, S. and D.W. Hosmer, *A Cautionary Note on the Use of the Grønnesby and Borgan Goodness-of-Fit Test for the Cox Proportional Hazards Model.* Lifetime Data Analysis, 2004. **10**(3): p. 283-291.
149. Blanche, P., J.F. Dartigues, and H. Jacqmin-Gadda, *Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks.* Stat Med, 2013. **32**(30): p. 5381-97.
150. Kamarudin, A.N., T. Cox, and R. Kolamunnage-Dona, *Time-dependent ROC curve analysis in medical research: current methods and applications.* BMC Medical Research Methodology, 2017. **17**(1): p. 53.
151. Heagerty, P.J. and Y. Zheng, *Survival Model Predictive Accuracy and ROC Curves.* Biometrics, 2005. **61**(1): p. 92-105.
152. Saha, P. and P.J. Heagerty, *Time-Dependent Predictive Accuracy in the Presence of Competing Risks.* Biometrics, 2010. **66**(4): p. 999-1011.
153. Bansal, A. and P.J. Heagerty, *A Tutorial on Evaluating the Time-Varying Discrimination Accuracy of Survival Models Used in Dynamic Decision Making.* Medical Decision Making, 2018. **38**(8): p. 904-916.
154. Martínez-Camblor, P. and N. Corral, *A general bootstrap algorithm for hypothesis testing.* Journal of Statistical Planning and Inference, 2012. **142**(2): p. 589-600.
155. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
156. Delgado-Rodríguez, M. and J. Llorca, *Bias.* Journal of Epidemiology and Community Health, 2004. **58**(8): p. 635.
157. Holmen, J., et al., *[A health survey in Nord-Trondelag 1984-86. Participation and comparison of attendants and non-attendants].* Tidsskr Nor Laegeforen, 1990. **110**(15): p. 1973-7.
158. Langhammer, A., et al., *The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms.* BMC Medical Research Methodology, 2012. **12**: p. 143-143.
159. Shirtcliffe, P., et al., *COPD prevalence in a random population survey: a matter of definition.* The European respiratory journal, 2007. **30**(2): p. 232-239.
160. Vollmer, W.M., et al., *Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study.* Eur Respir J, 2009. **34**(3): p. 588-97.
161. Halvorsen, T. and P.E. Martinussen, *The geography of chronic obstructive pulmonary disease: a population-based study of Norway.* Soc Sci Med, 2014. **111**: p. 25-34.
162. Feenstra, T.L., et al., *The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands.* Am J Respir Crit Care Med, 2001. **164**(4): p. 590-6.
163. Browatzki, A., C.S. Ulrik, and P. Lange, *Prevalence and severity of self-reported asthma in young adults, 1976–2004.* European Respiratory Journal, 2009. **34**(5): p. 1046.
164. Backman, H., et al., *Prevalence trends in respiratory symptoms and asthma in relation to smoking - two cross-sectional studies ten years apart among adults in northern Sweden.* World Allergy Organization Journal, 2014. **7**(1): p. 1.
165. Norwegian Institute of Public Health. *Asthma and allergy in Norway - Public health report 2014. https://www.fhi.no/en/op/public-health-report-2014/health--disease/asthma-and-allergy-in-norway---publ/#preventing-symptoms-, updated 18 Apr 2016 (accessed 05 Aug 2017).*

166. Johannessen, A., et al., *Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population.* Int J Tuberc Lung Dis, 2005. **9**(8): p. 926-32.
167. Lindberg, A., et al., *Seven-Year Cumulative Incidence of COPD in an Age-Stratified General Population Sample.* CHEST. **129**(4): p. 879-885.
168. van Durme, Y., et al., *Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study.* Chest, 2009. **135**(2): p. 368-377.
169. Gupta, R.P. and D.P. Strachan, *Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies.* BMJ Open, 2017. **7**(7).
170. Mannino, D.M., D.E. Doherty, and A. Sonia Buist, *Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study.* Respiratory Medicine, 2006. **100**(1): p. 115-122.
171. Selmer, R., et al., *NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction.* Eur J Prev Cardiol, 2017. **24**(7): p. 773-782.
172. Bland, J.M. and D.G. Altman, *The logrank test.* BMJ (Clinical research ed.), 2004. **328**(7447): p. 1073-1073.
173. Mandrekar, J.N., *Receiver Operating Characteristic Curve in Diagnostic Test Assessment*. Journal of Thoracic Oncology, 2010. **5**(9): p. 1315-1316.
174. Menezes, A.M., et al., *The PLATINO study: description of the distribution, stability, and mortality according to the Global Initiative for Chronic Obstructive Lung Disease classification from 2007 to 2017.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 1491-1501.
175. Marcoa, R., et al., *Classification of Chronic Obstructive Pulmonary Disease (COPD) according to the new Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017: Comparison with GOLD 2011.* Copd, 2018. **15**(1): p. 21-26.
176. *Le, L.A.K., Johannessen, A., Hardie, J.A., Johansen, O.E., Gulsvik, A., Vikse, B.E., and Bakke, P., Prevalence and prognostic ability of the GOLD 2017 classification compared to the GOLD 2011 classification in a Norwegian COPD cohort. Int J Chron Obstruct Pulmon Dis, 2009. 14: p. 1639-55.*

Appendix

Paper I - IV