COPD Patients' Vulnerability to Detachment from the Workforce and Their Employment Status' Association with Mortality and Treatable Traits

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Dissertation submitted

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ENGLISH SUMMARY

This Ph.D. includes four studies regarding chronic obstructive pulmonary disease (COPD) patients and workforce connection, with the aim to identify subgroups of patients vulnerable to negative health- and work outcomes. Study 1, 2, and 3 uses nationwide Danish registry data. Study 4 uses data obtained through questionnaires and clinical measurements from the Netherlands.

The first study explores how workforce status at first AECOPD hospital admission is associated with AECOPD readmission and mortality. The study included COPD patients age 35-59. Those not working were found to have a higher likelihood of readmission and death compared to those who were working.

The second study explores how the choice of voluntary early retirement affects mortality. This study shows that individuals who have COPD are more likely to choose voluntary early retirement. Furthermore, those who choose voluntary early retirement have a higher mortality compared to those who do not choose voluntary early retirement, if the benefit is chosen within the first year the benefit becomes available. These findings may be explained by an unhealthy selection bias. The two first studies confirm that individuals with COPD outside the workforce are vulnerable subgroups with regards to health outcomes.

The third study aims at identifying COPD patients at risk of delayed return to work and early retirement following the first AECOPD admission. Patients aged 35-59 who were part of the workforce were included and followed-up for three years. Return to work was high, with the majority of individuals returning within the first 4 week following admission. Early retirement happens steadily over time and individuals who are older, have more comorbidity, are living alone, and receive combination inhalation therapy are at risk of early retirement. This study confirms that individuals vulnerable to early retirement can be identified.

The fourth study explores treatable traits in patients with COPD without paid work, compared to those with paid work. COPD patients without paid work are found to have more treatable traits like lower exercise capacity, more dyspnea, higher exacerbation frequency, and lower daily activity. This indicates that interventions to prevent detachment to the work force may be a possibility.

The Ph.D. thesis hereby identify workforce connection as a socioeconomic marker of poor prognosis, identifying vulnerable patients and suggesting potential areas of intervention for the vulnerable subgroups. Future studies should explore if intervention may improve the vulnerable patients' clinical prognosis either through improved workforce connection or by improving treatable traits.

DANSK RESUME

Denne ph.d. undersøger patienter med kronisk obstruktiv lungesygdom (KOL) og arbejdsmarkedstilknytning i fire artikler, med det formål at undersøge helbredseffekt at arbejdsmarkedstilknytning, eller mangel på samme, samt undersøge potentielle modificerbare faktorer hos patienter uden for arbejdsmarkedet. Artikel 1, 2 og 3 bruger landsdækkende danske registerdata. Artikel 4 bruger data fra Holland, indsamlet gennem spørgeskemaer og kliniske målinger.

Første artikel undersøger, hvordan arbejdsmarkedstilknytning ved første hospitalsindlæggelse med akut forværring af KOL (AFKOL) er forbundet med AFKOL genindlæggelse og dødelighed. Artiklen omfatter KOL-patienter i alderen 35-59. En højere sandsynlighed for genindlæggelse og død blev observeret hos dem der ikke var i arbejde sammenlignet med dem, der arbejdede.

Anden artikel undersøger, om individer, der vælger efterløn, har højere dødelighed i forhold til dem der ikke vælger dette. Artiklen viser, at KOL-patienter oftere vælger efterløn. Dem, der vælger efterløn indenfor det første år fra ydelsen kan vælges, har en højere dødelighed sammenlignet med dem, der ikke vælger efterløn. En mulig forklaring på dette er sundhedsselektions bias. De to første artikler bekræfter, at personer med KOL uden for arbejdsmarkedet er helbredsmæssigt sårbare.

Den tredje artikel undersøger, om KOL-patienters tilbagevenden til arbejdsmarkedet og førtidspension efter første AFKOL-indlæggelse. Patienter i alderen 35-59 og i arbejde ved første indlæggelse, blev inkluderet i studiepopulationen og fulgt i 3 år. Størstedelen af patienterne returnerede til arbejdsmarkedet inden for de første 4 uger. Frafald til førtidspension var stabil over tid. Patienter, der er ældre, har flere komorbiditeter, bor alene og modtager kombineret inhalationsbehandling er i højere risiko for at modtage førtidspension. Denne artikel bekræfter at sårbare KOL-patienter i risiko for at forlade arbejdsmarkedet til førtidspension.

Den fjerde artikel undersøger behandlingskarakteristika hos KOL-patienter uden lønnet arbejde, sammenlignet med KOL patienter med lønnet arbejde. KOL-patienter uden lønnet arbejde har i studiet nedsat træningskapacitet, mere dyspnø, højere frekvens af AFKOL og lavere daglig aktivitet. Dette indikerer, at intervention muligvis kan forhindre patienters frafald fra arbejde.

Ph.d.-afhandlingen identificerer hermed manglende arbejdsmarkedstilknytning som en socioøkonomisk markør for dårlig prognose, identificerer sårbare patienter og foreslår potentielle indsatsområder for de sårbare undergrupper. Fremtidige undersøgelser bør undersøge, om intervention kan forbedre de sårbare patienters kliniske prognose, enten gennem forbedret arbejdsmarkedstilknytning eller ved at forbedre behandlingstiltag.

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PAPERS INCLUDED IN THE THESIS

Study I:

Authors: Peter Ascanius Jacobsen, Kristian Hay Kragholm, Christian Torp-Pedersen, Daisy J.A. Janssen, Martijn A Spruit, Ulla Møller Weinreich

Title: *"Employment Status, Readmission and Mortality After Acute Exacerbation of COPD"* International Journal of Chronic Obstruct Pulmonary Disease. (1)

Study II:

Authors: Peter Ascanius Jacobsen, Kristian Hay Kragholm, Mikkel Porsborg Andersen, Christian Torp-Pedersen, Ulla Møller Weinreich

Title: *"Voluntary early retirement and mortality in patients with and without chronic diseases. A nationwide Danish Registry study"* (in review)

Study III:

Authors: Peter Ascanius Jacobsen, Kristian Hay Kragholm, Christian Torp-Pedersen, Ulla Møller Weinreich

Title: *"Return to work and early retirement from the workforce after first admission with acute exacerbation of chronic obstructive pulmonary disease - a Danish Nationwide registry cohort study using a retrospective follow-up design"* (in review)

Study IV:

Authors: Peter A. Jacobsen, Alex J. van 't Hul, Remco S. Djamin, Jeanine C. Antons, Marianne de Man, Ulla Møller Weinreich, Martijn A. Spruit, Daisy J.A. Janssen

Title: *"Characteristics and treatable traits of patients with chronic obstructive pulmonary disease (COPD) with and without paid employment"* Respiratory Research. (2)

LIST OF ABREVIATION

6MWD: Six-minute walk distance.

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease

ATC: Anatomical, therapeutic, chemical classification

BMI: Body mass index

BODE: Body mass index, airflow Obstruction Dyspnea, Exercise

CIS: Checklist individual strength.

COPD: Chronic obstructive pulmonary disease

FEV1: Forced expiratory volume in one second.

ICD-10: International classification of disease version 10

ICS: Inhaled corticosteroid

LAMA: Long-acting muscarinic antagonist

LABA: Long-acting β2-agonist

MRC: Medical research council score

SABA: Short acting beta agonist

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CHAPTER 1. INTRODUCTION

1.1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (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 and influenced by host factors including abnormal lung development." (3). The airflow limitation is defined as a chronic airflow obstruction with a forced expiratory volume in one second (FEV1)/ forced vital capacity (FVC) ratio below 70%. Symptoms include, but are not limited to, dyspnea, coughing, fatigue, muscle weakness, and cognitive impairment (3). Patients living with COPD may be impaired in varying degrees by their COPD disease with symptoms leading to a reduction in activities of daily living, limiting physical activity, and poor quality of life (4, 5).

COPD commonly develops after the age of 40 but is also seen in younger patients with incidence estimates in individuals 30-40 years old of 2.6 cases/1000/year (6-8). The prevalence of airway obstruction (FEV1/FVC < 70%) and respiratory symptoms in individuals age 30-39 who had above 10 cigarette pack years has been found to be 7.4% in a Danish population sample (9). The primary cause of COPD in high-income countries is cigarette smoking which through inflammation causes irreparable damage leading to airflow limitation (10, 11). Tobacco use is ranked the second highest risk factor for death in the Global Burden of Disease (2019) and is for approximately 86% of COPD patients in the general population in Copenhagen a prerequisite to the diagnosis (12, 13). Other predisposing factors exist such as air pollution and genetic predisposition (11). Lower socioeconomic status is associated with a higher frequency of COPD (14, 15). It is estimated that 8% of the Danish population have COPD with slightly more male than female patients (13, 16, 17). The prevalence on an international scale for men is 9% and for women 6% making the Danish distribution relatively high for women (18). The prevalence in patients above 35 years has been estimated to 17.4% (13). A large group (78%) among high-risk individuals (more than 10 package years) who fulfill spirometry criteria for COPD are undiagnosed (17).

1.2. ACUTE EXACERBATION

Acute worsening of symptoms requiring treatment is defined as AECOPD in the GOLD guidelines (3, 19). Exacerbations vary in degree of severity ranging from mild

exacerbations treatable with medication at home, to severe exacerbations requiring hospital admission with intensive care treatment and mechanical ventilation (20). Characteristics of patients experiencing severe AECOPD for the first time indicate some disease severity as explored by Balcells et al (21). They found patients to have a mean FEV1 of 49% predicted, 87% having a mMRC score above or equal to 2 and 50% had two or more comorbidities. Exacerbations causes disease progression and may lead to death hereby contributing to the morbidity and mortality in COPD patients (19, 22). The case fatality rate of AECOPD has been estimated at 15.6% (23). Approximately 26% die within one year and 60% within 5 years after a severe AECOPD (24, 25). The event of AECOPD hereby is of value when exploring outcomes for COPD patients as it represents both disease severity and prognosis in COPD patients.

1.3. TREATABLE TRAITS

A physiological decline in lung function occurs from around the age of 20-25 which makes COPD preventable but not reversable (26). Smoking cessation can, as a preventive measure, lead to modest increases in lung function and limit the decline in lung function (27). COPD, however, remains a chronic degenerative disease with permanent damage to the lungs (10). Treatment for COPD therefore aims at preventing further disease progression and improving patient symptoms and outcomes. As a way of targeting treatment, different domains of treatment exist known as the treatable traits (28, 29). These include traits such as physical activity, proneness to lung attacks, and body composition (29, 30). Clinical measures are used to identify treatable traits in research. Six minute walk distance (6MWD) and activity monitors are used to identify exercise capacity and daily activity respectively where both may be improved upon through pulmonary rehabilitation and medication (29, 31-33). AECOPD frequency may also be regarded as a treatable trait where pulmonary rehabilitation, self-management plans, and medical intervention may improve exacerbation frequency and severity (33-35). The general purpose of this approach is to improve patients' quality of life and prognosis by improving traits that may impact quality of life and clinical outcomes like admission and mortality negatively (29, 30).

The non-reversable damage to the lungs makes it paramount to implement treatment and preventive measures as early as possible to prevent development towards severe COPD. The focus of this PhD is to explore workforce connection in COPD patients and how this is associated with COPD patients' prognosis. Furthermore, to identify predictors of poor workforce connection as a way of detecting vulnerable COPD patients as early as possible.

CHAPTER 2. BACKGROUND

2.1. THE DANISH LABOUR MARKET

The Danish labour market system relies on a high flexibility, acknowledging the employers right to fire employees as they see fit (36). A part of this labour market model is an extensive public support system that supports those outside the workforce. This system includes educational, maternity, sick leave, unemployment, early voluntary retirement benefit, early retirement, "FLEXjob" and regular retirement.

Sick leave is available to individuals who due to sickness/disability cannot perform work. The first 30 days of sick leave is paid by the employer who in the case of sick leave of 30 days or longer can apply for reimbursement from the Danish social system (37).

Early retirement is available to individuals below age 65 who are no longer able to participate in the workforce due to mental or physical disability. This benefit is also referred to as disability pension (38).

Individuals with severely impaired work capability can apply for a "FLEXjob" where the Danish support system will ensure a minimum wage for individual who can work very limited (39).

The public support voluntary early retirement is in Danish called "efterløn" which directly translates to "after pay" (40). This benefit became available in 1979 as a way of letting individuals who due to physical or mental demanding work could retire at age 60 instead of 67 which at the time was the regular retirement age. This was done to make room for the younger generation where the unemployment rate was high. The rights to receive the benefit have changed over time and is currently available to individuals who are part of an unemployment insurance fund and who actively choose to contribute to the voluntary early retirement scheme. Payments into the scheme must start prior to the age of 30 and the benefit is only available if you are actively working when choosing to leave the workforce (41). If the benefit is chosen with less than 3 years till the regular retirement age a higher benefit is received. The age when the benefit becomes available has changed over time. During the time periods explored in this Ph.D. the voluntary early retirement age has been 60 years and the regular retirement age has been 65 years.

2.2. WORKFORCE CONNECTION IN COPD PATIENTS

2.2.1. UNEMPLOYMENT, ABSENTEEISM AND PRESENTEEISM IN COPD

COPD Patients have lower employment rates compared to healthy individuals and other patients with other chronic conditions with approximately 60% of individuals with COPD without paid work (42-45). In the general population approximately 20% of individuals between 18-64 are without work in Denmark (44). When exploring employment in only individuals above 40 years the differences diminish. Here 42.9% of non-COPD patients were not employed in a Latin-American cohort (42). A Californian study compared asthma, COPD, "other chronic conditions" and no chronic conditions groups and found that COPD patients had the lowest employment rates (46.5%) followed by "other chronic conditions" (66.2%), asthma (67.6%) and no chronic conditions (71.1%) (45). Significant differences in age were, however, seen between the groups making the estimates somewhat biased. Nonetheless, clear indications of poor workforce connection in COPD patients persist across studies and nationalities. This is to some extent explained by a limited work capability in COPD patients compared to healthy individuals and individuals with "other chronic diseases" (45). The likelihood of being in paid work has been explored in COPD patients, where higher age, lower educational level, higher BODE index, and occupational exposure to vapors, gasses, dust, and fumes associated with a decreased likelihood of paid work (43). Furthermore, MRC score, airflow obstruction, CAT score, and exacerbation frequency were found in univariate analysis to be associated with not being in paid work (43).

The COPD patients who are part of the workforce have more presenteeism (working while sick impacting performance) and absenteeism (absence from work) compared to individuals without COPD. Presenteeism and absenteeism has been estimated twice as high in patients with COPD compared to healthy individuals (46-48). When comparing COPD patients with other chronic conditions like asthma, diabetes, back/neck pain, cancers and migraines COPD comes with higher rates of presenteeism and absenteeism (49). Sick leave is also higher in those with moderate to severe airflow limitation as seen in a Japanese study with 54% reporting one or more days of sick leave within a 12 month period which was 39.5% in those without airflow limitation (50). This effect is attenuated by disease severity as Wacker et al. demonstrated in a German cohort grading COPD according to FEV1 as grade 1 (FEV1 $\geq$ 80%), 2 (FEV1 < 80% and $\geq$50%), grade 3 (FEV1 <50% and $\geq$30%) and grade 4 (FEV1 < 30) (51). This study found that 70-76% of COPD patients experience sick leave during a 12 months period compared to 44% among controls without COPD.

Those without COPD had seven sick leave days on average, compared to 31, 26, 34, and 40 sick leave days in COPD patients grade 1, 2, 3, and 4 respectively.

COPD patients' workforce connection has as shown been explored extensively with the conclusion that COPD patients have a very poor workforce connection which comes at great cost for society. Studies exploring the impact of AECOPD on patients' workforce connection using a follow-up study design with regards to return to work are very limited with only one of poor quality to the best of my knowledge available (52). These studies are much need to identify patient vulnerable for poor workforce outcomes so relevant interventions can be implement.

2.2.2. WORKFORCE CONNECTIONN AS A SOCIOECONOMIC INDICATOR

Different factors play a role for in an individuals' in general and COPD patients workforce connection. In general people with higher education are more likely to have paid employment and higher education is associated with higher income (53, 54). Both education and income have been used as socioeconomic predictors of readmission and mortality in COPD patients with an inverse association in that low income and low education is associated with higher readmission and mortality rates (38, 55).

The workforce connection's effect on AECOPD, admission to the hospital and mortality in COPD patients has previously been explored by Tøttenborg et al. (38). They investigated COPD patients' workforce connection as employed, pensioners, voluntary early retirement, unemployed and disability pension (38). Those employed were used as the reference group. A significantly lower frequency of exacerbations was observed in people who were unemployed in the fully adjusted model. A higher frequency was observed in patients receiving disability pension and regular retirement in the fully adjusted model. No difference was observed in those who were receiving voluntary early retirement. A similar pattern of likelihoods was found with regards to admission and death. These models did not show significant beneficial effects for unemployment.

The link between health outcomes and socioeconomic factors must be related to positive and negative health behavior associated with the different socioeconomic layers as the status does not hold any risk in itself. The extensively researched and most likely connection between the two is that poor health status is associated with poor workforce connection as summed up in the review by Nordström et. al. (56). The causal relationship between health and poor workforce connection is however not clear. A study by Böckerman et al. explored this and found a selection bias in that

those who are working who become unemployed have a preexisting poor health status from employment and those who from unemployment who were reemployed had a better health status (57). These findings do not exclude that possible negative effects exist with unemployment they do however show that an unhealthy selection bias exists in the unemployed.

2.2.3. POSITIVE AND NEGATIVE EFFECTS ASSOCIATED WITH RETIREMENT.

The behavior of patients with work force detachment in terms of retirement, early retirement, voluntary early retirement, and unemployment enforce may be different. However, these different ways of detachment have the shared denominator of not being active in paid work. Multiple studies have explored the effects of retirement across different health related outcomes (58). Among these is physical activity and the results from these studies are not unanimous. Retirement from physically demanding work has been associated with an activity decrease in opposition to an increase in activity when retiring from sedentary work, which is supported by an observed increase in BMI following retirement from physically demanding work (59, 60). Studies find expectedly that leisure time activities increase following retirement, as work limits the hours per day that leisure time activities are possible (61, 62). However, an increase in sedentary living is also seen which is associated with a higher mortality in COPD patients (62-65). Increase in physical activity has been associated with a decreased likelihood of early retirement and those decreasing their physical activity have an increased risk of early retirement (66).

Changes in smoking behavior following retirement has also been explored. Only a few studies indicate an increase in smoking behavior with the most studies indicating no or a higher likelihood of smoking cessation (58, 67-69). Alcohol consumption and diet has furthermore been explored with diverging results (58).

The health impact of retirement is therefore likely a mix of harmful and beneficial effects making exploration of the effect of retirement om mortality difficult, as it is impacted from many different sources. Studies exploring treatable traits where intervention may be possible for COPD patients outside the workforce are lacking. These studies may help the understanding of the association between unemployment and COPD but also suggest potential areas of intervention to improve upon.

2.2.4. EARLY RETIREMENT (DISABLILITY PENSION) AND VOLUNTARY EARLY RETIREMENT

Disease severity in COPD patients has been associated with a higher likelihood of early retirement (70, 71). This is in a Danish context not surprising, as the benefit early retirement's is only available to those with an inability to work. Furthermore, early retirement is associated with mortality (38, 72). Prediction of who, among COPD patients, are at risk of early retirement would hereby be valuable. If preventive interventions can be implemented this may be valuable from a patient perspective, as a way of predicting a functional decline in patients at risk of early retirement (70, 71). From a societal perspective, intervention may help avoid the public expenses associated with early retirement if detachment can be avoided (70). In addition, it would. Studies predicting early retirement using a follow-up design in COPD patients are not available.

Voluntary early retirement, however, represents a workforce group which is somewhat different, in that it is voluntary. Different methods have been implemented to try to isolate potential beneficial effects of voluntary early retirement on mortality with diverging results. A number of these studies have been explored in a meta-analysis showing no difference in survival (73). The choice has previously been associated with poor self-rated health and mortality compared to those remaining in work (72, 74). With COPD being associated with poor health status it is likely that more COPD patients choose voluntary early retirement and hereby making voluntary early retirement an indicator of poor health. It is however also possible that when exploring COPD patients as a subgroup poor health is universal and that this would limit the association between voluntary early retirement and mortality. Studies exploring the effect of voluntary early retirement in COPD patients specifically in a population eligible for voluntary early retirement are however lacking.

2.1. HYPOTHESIS AND AIMS

FIRST STUDY HYPOTHESIS:

> COPD patients outside the workforce are more vulnerable to readmissions and have higher mortality compared to COPD patients' part of the workforce.

AIM: Explore if workforce status is associated with readmission and mortality and hereby identify if patients outside the workforce are considered a vulnerable subgroup of COPD patients.

SECOND STUDY HYPOTHESIS:

Individuals choosing to leave the workforce voluntarily are more likely to have comorbidity and have a higher mortality across disease and demographic subgroups compared to those who do not choose to leave voluntarily.

AIM: Explore which individuals are at risk of choosing voluntary early retirement and identifying potential beneficial and harmful associations to mortality for individuals leaving the workforce voluntarily.

THIRD STUDY HYPOTHESIS:

COPD patients are vulnerable to delayed return to work and permanent detachment exist following hospitalization with AECOPD.

AIM: Characterize patients at risk of delayed return to work and permanent detachment.

FOURTH STUDY HYPOTHESIS:

COPD patients without work have more treatable traits than patients' part of the workforce.

AIM: Explore potential areas where intervention may improve patients outside the workforce.

THESIS HYPOTHESES

COPD patients below 65 years are vulnerable to detachment from the workforce and patients outside the workforce a poor prognosis.

AIM: Identify vulnerable COPD patients and patients at risk of becoming vulnerable using workforce connection (Thesis aim).

CHAPTER 3. METHOD

3.1. DANISH REGISTRY STUDIES

This section will describe the methods used across the studies conducted using the Danish national registries (study 1, 2 and 3). Methods for the study 4 which uses Dutch data will be described separately.

3.1.1. STUDY SETTING

The Danish social system provides free healthcare and education as well as different social support benefits including unemployment-, sick leave- and early retirement benefit, through the Danish tax paying system. All Danish citizens have a unique Civil Personal Registration number which makes identification of individuals across multiple registries possible (75).

3.1.2. STUDY DESIGN

All registry studies included are retrospective cohort studies using a follow-up design.

3.1.3. DATA SOURCES

The following registries were used to gather information for the Danish registry studies:

THE NATIONAL PATIENT REGISTRY

Information on all public hospital contacts in Denmark including outpatient visits and hospitalizations including admission date, discharge date, and ICD-10 code related to hospital contact (76).

THE NATIONAL PRESCRIPTION REGISTRY

Information on all prescriptions redeemed from Danish pharmacies including date of medication collection and medication type identified by ACT codes (77).

THE DANISH NATIONAL LABOUR MARKET DATABASE (DREAM)

Information on all public social benefits including but not limited to educational, unemployment, sick-leave, and early retirement benefit. The accuracy of self-support has previously been explored with a predictive value of 98,2% (78).

THE DANISH CAUSE OF DEATH REGISTRY

Information on time of death (79).

THE STATISTICS OF DENMARK

Information on age, sex, educational level, and income level (75).

3.1.4. VARIABLE DEFINITIONS

Variables are defined in the same way across the studies unless specified otherwise and are as follows.

3.1.4.1 Workforce connection

The specific codes of how workforce connection was characterized is show in appendix A. The general definitions are as follows:

WORKING

Not receiving public support or receiving benefits characterized as work (e.g., educational support and certain benefits which indicate active work)

UNEMPLOYED

Receiving unemployment benefits.

SICK LEAVE

Patients receiving sick leave benefit 3 out of 4 weeks prior to index time.

EARLY RETIREMENT

Patients receiving disability pension, or the public support called "FlexJob" which is only available with severely impaired work

capability. This is similar to what other studies classify as disability pension.

VOLUNTARY EARLY RETIREMENT

The public benefit voluntary early retirement (efterløn) was during the study period available from the age of 60 until 64 to people who were part of an unemployment insurance fund, who actively pays into the voluntary early retirement scheme.

3.1.4.2 Acute exacerbation of chronic obstructive pulmonary disease

AECOPD was defined as an admission with a primary discharge diagnosis of COPD (DJ44) excluding asthmatic bronchitis (DJ448B) or a primary discharge diagnosis of pneumonia (DJ13-DJ18) or acute respiratory insufficiency (DJ96) with a secondary diagnosis of COPD as above. These criteria have previously been validated in the National Patient Registry with a positive predicative value of 92% (80).

3.1.4.3 Comorbidity

All comorbidities were gathered using ICD-10 codes in the National Patient Registry 5 years prior to index time. Prescription data are furthermore used to identify diabetes. Anxiety and depression are identified using the National Psychiatric registry together with prescription data on anxiolytics and antidepressants respectively. Comorbidity selection differed across the different studies but were selected from either the Charlson index, COTE index or mentioned in the GOLD guidelines (3, 81, 82). Healthy was defined as patients without comorbidity or any prescription for medication (see appendix B for details on which ICD-10 codes are included in comorbidity).

3.1.4.4 Medication use

Inhaled obstructive airway medication was defined as any prescription redeemed 6 months prior to index time. Any combinations LAMA, LABA or ICS were grouped into “LAMA OR LABA only”, “ICS only”, “LABA & ICS OR LAMA & ICS”, “LAMA & LABA & ICS”, “SABA only”, and “No inhalation medication”. All groups were exclusive groups meaning that participants were only able to be in one group. The definition leaves the possibility that non-adherent patients and undiagnosed patients are grouped together.

3.1.4.5 Educational level

Educational level is divided into 4 categories of short, medium, long and very long corresponding to the International Standard Classification of Education (ISCED) levels 1-2, 3 and 5, 6, and 7 or above respectively. Education level 4 does not exist in the Danish education system.

3.1.4.6 Income

Divided according to population into low (0-25 percentile), medium (25-75 percentile) and high (75-100 percentile).

3.2. STUDY 4

3.2.1. STUDY SETTING

The study was conducted in the Netherlands with information gathered from three outpatient clinics in the Netherlands at Amphia hospital, Breda, Radboudumc, Nijmegen, and Bernhoven hospital, Uden between 2013 and 2018.

3.2.2. STUDY DESIGN

This study uses a cross-sectional cohort study design.

3.2.3. DATA SOURCES

Data was gathered on patients referred for the first time to an outpatient clinic with a diagnosis of COPD. Questionnaires were used including Checklist Individual Strength fatigue score (CIS) together with measurement on FEV1, 6MWD, activity monitors, and questionnaires.

3.2.4. VARIABLES

Treatable traits were explored in the form of dyspnea (MRC score), exercise capacity (6MWD), activity level (steps above 5000 per day), fatigue (CIS score), smoking status (active), abnormal BMI (<21 or >30), and exacerbations (≥ 2).

Age, sex, pulmonary function (FEV1), and educational level were included in the analysis of the likelihood of being without paid work.

3.3. STATISTICS

Continuous data are displayed using means and standard deviations when normally distributed and median and 25th and 75th percentiles. Categorical data are displayed using counts and percentages.

Incidence rates are displayed using cumulative incidence plots.

Logistic regression and Cox regression were used to explore outcomes adjusting for relevant confounders of age, sex, educational level, income, and comorbidity when appropriate in the respective studies.

3.4. STUDY POPULATION AND STUDY SPECIFIC CONSIDERATIONS

3.4.1. STUDY I: "EMPLOYMENT STATUS, READMISSION AND MORTALITY AFTER ACUTE EXACERBATION OF COPD" (1)

Patients were included at first hospitalization with AECOPD between 1999-2014, age 35-59, with no previous diagnosis of asthma.

Logistic regression was used to explore AECOPD readmission and mortality rates. Analysis of readmission did not account for competing risk of death.

3.4.2. STUDY II: "VOLUNTARY EARLY RETIREMENT AND MORTALITY IN PATIENTS WITH AND WITHOUT CHRONIC DISEASES. A NATIONWIDE DANISH REGISTRY STUDY" (IN REVIEW)

This study includes all Danish citizens who had their 60th or 62nd birthday between 2000-2015. Only individuals not receiving any benefit at the time of their 60th or 62nd birthday were included. Furthermore, individuals not part of an unemployment insurance fund was excluded.

Subgroups were explored on two levels of "disease subgroups" and "demographic subgroups". Disease subgroups included healthy, and patients with COPD, heart failure and diabetes. Demographic subgroups included sex (male and female), education ("short" and "medium or above"), and income ("low income" and "high income").

3.4.3. STUDY III: "RETURN TO WORK AND EARLY RETIREMENT FROM THE WORKFORCE AFTER FIRST ADMISSION WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE - A DANISH NATIONWIDE REGISTRY COHORT STUDY USING A RETROSPECTIVE FOLLOW-UP DESIGN." (IN REVIEW)

Patients supporting themselves or receiving benefits characterized as work at the time of first hospitalization with AECOPD between 1999-2014, age 35-59, with no previous diagnosis of asthma were included.

Voluntary early retirement and death were, in a cox regression model for likelihood of early retirement, treated as competing risk and hereby censored to avoid patients contributing with time in the analysis where return is highly unlikely or impossible. The choice to censor for voluntary early retirement is that this benefit does not necessarily indicate a functional decline.

3.4.4. STUDY IV: "CHARACTERISTICS AND TREATABLE TRAITS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) WITH AND WITHOUT PAID EMPLOYMENT" (2)

Patients were included at first referral to an outpatient clinic with COPD. COPD diagnosis was confirmed through spirometry with a FEV1/FVC ratio below 70%. Patients age 65 or above were excluded.

CHAPTER 4. RESULTS

The following results section will focus on answering the hypotheses listed in the hypothesis and aims section and will be listed accordingly.

4.1.1. FIRST HYPOTHESIS – STUDY I

COPD PATIENTS OUTSIDE THE WORKFORCE ARE MORE VULNERABLE TO READMISSIONS AND HAVE HIGHER MORTALITY COMPARED TO COPD PATIENTS' PART OF THE WORKFORCE

11,850 patients with first time AECOPD were included in *study I*. The distribution of workforce status at first admission was with 3563 working, 1368 unemployed, 840 on sick leave and 6079 on early retirement benefit. The event rates for readmission and mortality are shown in figure 1 and figure 2.

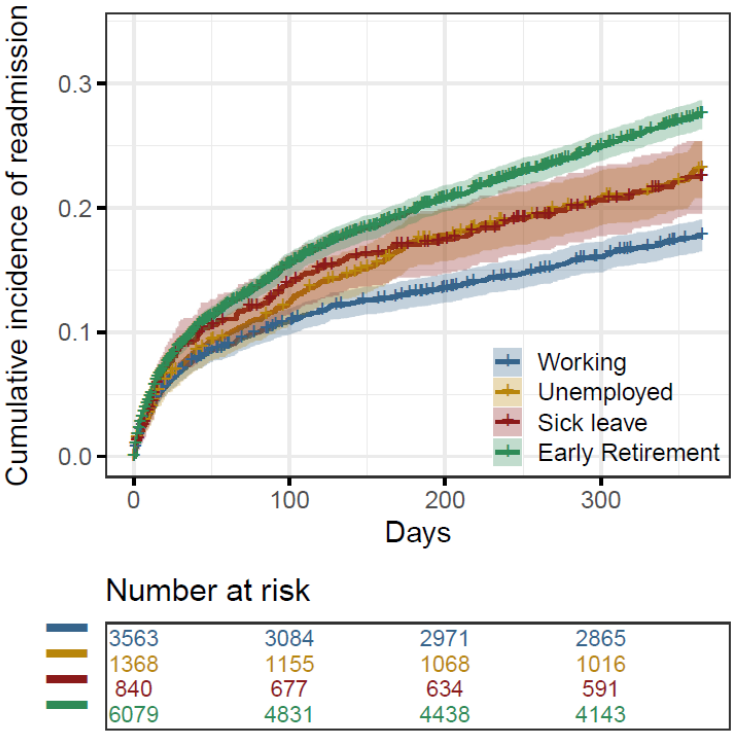

Figure 1. Cumulative incidence curves for mortality. At risk table display COPD patients who has not died.(1)

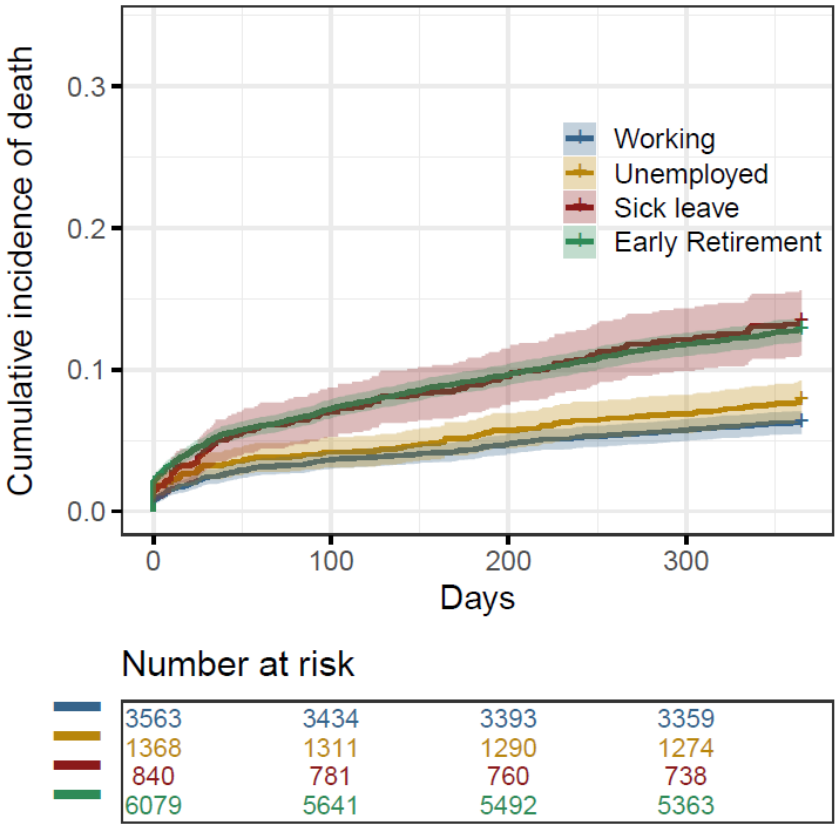

Figure 2 Cumulative incidence curves for readmission. At risk table display COPD patients who has not been readmitted or died(1).

The highest readmission rates over time are observed in the early retirement group and the highest mortality rates are observed in the early retirement and sick leave groups.

In the study 1 unemployment and early retirement was associated with readmission as shown in figure 3. Sick leave and early retirement was associated with mortality as shown in figure 3.

Variable	Days	N	Events	OR(95% CI)	P-values
Readmission					
Working	30	3,563 (30.1)	244 (25.8)	1.00 (1.00−1.00)	1.0000
	90		368 (24.9)	1.00 (1.00−1.00)	1.0000
	365		618 (23.1)	1.00 (1.00−1.00)	1.0000
Unemployed	30	1,368 (11.5)	99 (10.5)	1.07 (0.84−1.37)	0.5779
	90		155 (10.5)	1.14 (0.93−1.40)	0.2050
	365		305 (11.4)	1.44 (1.22−1.68)	<0.001
Sick leave	30	840 (7.1)	74 (7.8)	1.31 (0.99−1.73)	0.0544
	90		106 (7.2)	1.20 (0.95−1.52)	0.1293
	365		178 (6.7)	1.18 (0.98−1.44)	0.0863
Early retirement	30	6,079 (51.3)	529 (55.9)	1.26 (1.06−1.49)	0.0078
	90		849 (57.4)	1.33 (1.16−1.53)	<0.001
	365		1575 (58.9)	1.48 (1.33−1.66)	<0.001
Mortality					
Working	30	3,563 (30.1)	85 (18.7)	1.00 (1.00−1.00)	1.0000
	90		123 (19.0)	1.00 (1.00−1.00)	1.0000
	365		223 (18.2)	1.00 (1.00−1.00)	1.0000
Unemployed	30	1,368 (11.5)	44 (9.7)	1.16 (0.79−1.69)	0.4577
	90		55 (8.5)	1.00 (0.71−1.40)	0.9870
	365		107 (8.8)	1.12 (0.87−1.44)	0.3661
Sick leave	30	840 (7.1)	36 (7.9)	1.17 (0.77−1.77)	0.4632
	90		56 (8.7)	1.29 (0.91−1.82)	0.1487
	365		112 (9.2)	1.57 (1.21−2.04)	<0.001
Early retirement	30	6,079 (51.3)	289 (63.7)	1.39 (1.07−1.80)	0.0144
	90		413 (63.8)	1.37 (1.09−1.70)	0.0059
	365		780 (63.8)	1.48 (1.25−1.75)	<0.001

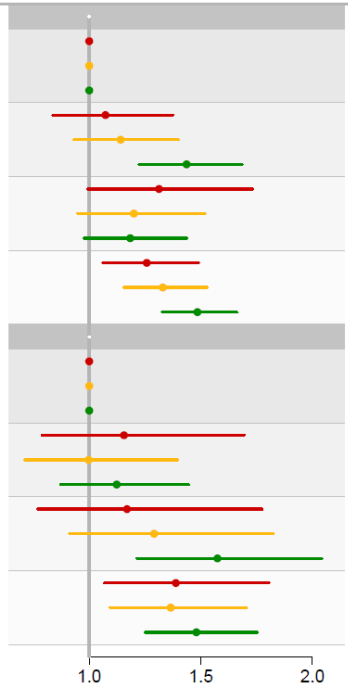

Figure 3 Multivariable logistic regression of 30-, 90- and 365-days' readmission and mortality following first admission with AECOPD. 30-, 90- and 365-days mortality is indicated by red, yellow and green respectively. Output in figure is adjusted for age, sex, education, cohabitation status, lung cancer, other cancer, pulmonary fibrosis, atrial fibrillation/atrial flutter, heart failure, ischemic heart disease, cerebrovascular disease, gastric ulcer, chronic kidney failure, diabetes, anxiety, depression and inhalation medication combination(1).

4.1.2. SECOND HYPOTHESIS – STUDY II

INDIVIDUALS CHOOSING TO LEAVE THE WORKFORCE VOLUNTARILY ARE MORE LIKELY TO HAVE COMORBIDITY AND HAVE A HIGHER MORTALITY ACROSS DISEASE AND DEMOGRAPHIC SUBGROUPS COMPARED TO THOSE WHO DO NOT CHOOSE TO LEAVE VOLUNTARILY.

This study includes 627,278 individuals at their 60th birthday and 379,196 at their 62nd birthday. Figure 4 shows the cumulative incidence of patients choosing voluntary early retirement from their 60th birthday. The figure shows a peak of individuals choosing voluntary early retirement at age 60 and 62.

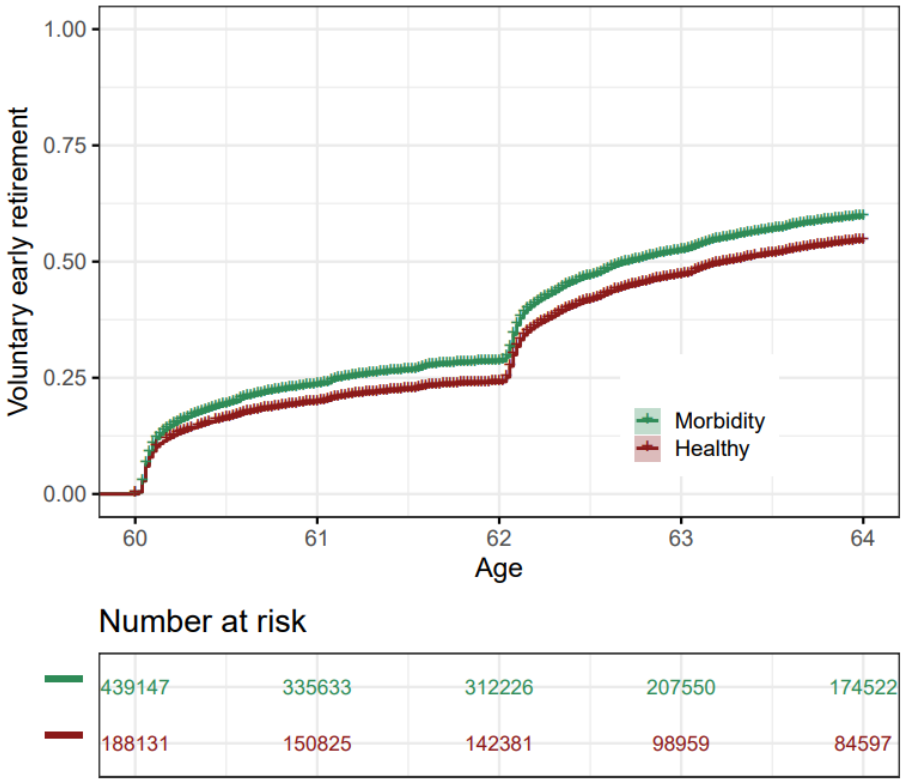

Figure 4. Cumulative incidence from age 60 till early voluntary retirement in weeks.

The likelihood of choosing voluntary early retirement is displayed in figure 5. A lower likelihood for choosing voluntary early retirement is observed in individuals with

higher education, male sex, higher income, and categorized as healthy. An increased risk is seen with low income and in patients with COPD and heart failure.

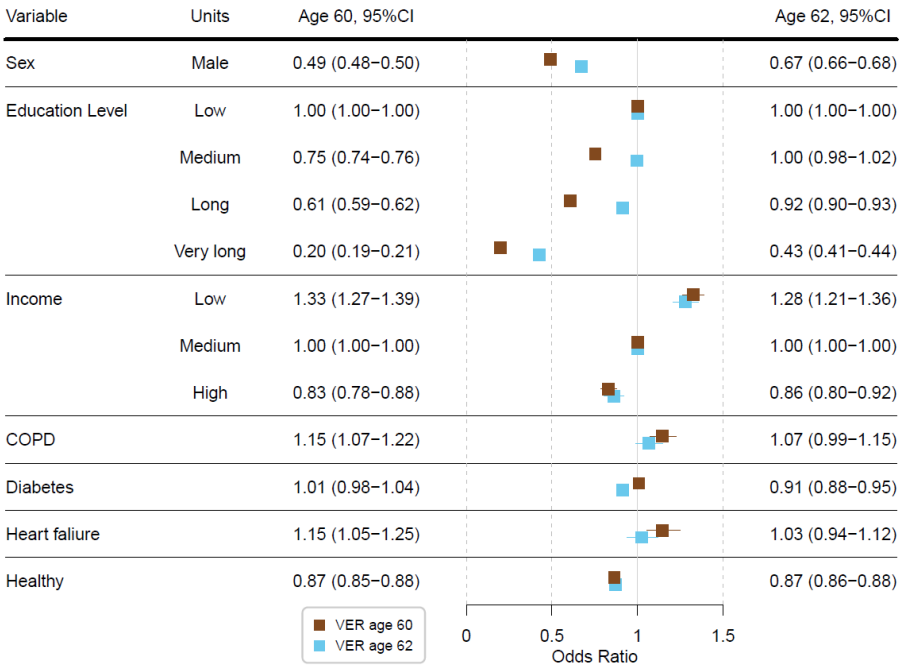

Figure 5. Logistic regression model of the likelihood of choosing voluntary early retirement (VER) benefit with all variables displayed included in the model. Estimates are odds ratio

Three-year mortality likelihood from age 60 and 62 is shown in figure 6. Individuals choosing voluntary early retirement at age 60 have an increased three-year mortality likelihood in total and subgroups of female, male, short education, medium/long education, low income and high income when not subdividing into disease categories. An increased mortality risk is also seen for all disease subgroups in the age 60 cohort of healthy, COPD, heart failure, and diabetes when not subdividing into demographic subgroups. Demographic and disease subgroups combined also reveal significant values in many subcategories with some failing to reach significance but indicating a tendency towards an increased mortality. Only females with COPD and the "low-income + heart failure" subgroups had point estimates very close or equal to one in the age 60 cohort. For those choosing voluntary early retirement at age 62 the choice is not significantly associated with an increased mortality except for COPD patients with medium or high educational level. The COPD subgroup in general have higher odds ratio estimates compared to other subgroups of diseases/healthy.

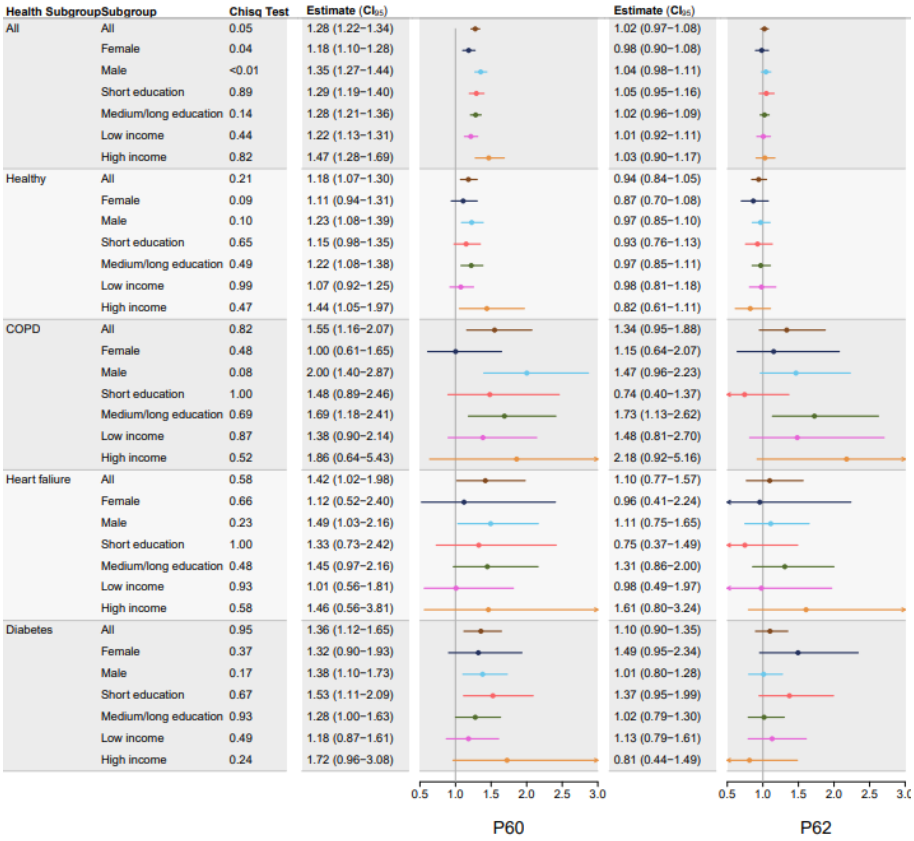

Figure 6. Logistic regression model of the likelihood of three-year mortality in the P60 (inclusion at age 60) and P62 (inclusion at age 62) cohorts stratified according to disease categories and subgroups of male, female, low/medium education level and long/very long education level. All models are adjusted for education level, sex and Charlson comorbidity index in accordance with subgroup division. Estimates are displayed as odds ratios. Chi-sq test show the p-value of the group difference comparing voluntary early retirement rates in the two cohorts and their death rate. All significant P-values indicate a favorable outcome for those choosing voluntary early retirement at age 62. Subgroup colors; gray = All; pink = female; blue = male; yellow = education level low and medium; green = education level long and very long.

4.1.3. THIRD HYPOTHESIS – STUDY III

COPD PATIENTS VULNERABLE TO DELAYED RETURN TO WORK AND PERMANENT DETACHMENT EXIST FOLLOWING HOSPITALIZATION WITH AECOPD.

Study 3 includes 3769 first time hospitalised AECOPD patients. Cumulative incidence of three-year return to work and early retirement is shown in figure 7. Return to work within the first four weeks following admission was seen in 66.7% (2515/3769) whereas 5.4% (202/3769) did not return to work during the three-year follow-up. Early retirement occurs steadily over time with 17.0% (641/3769) retiring early during follow-up. Of the patients not returning to work 4.5% (171/3769) received early retirement benefit during follow-up, accounting for 26.7% (171/641).

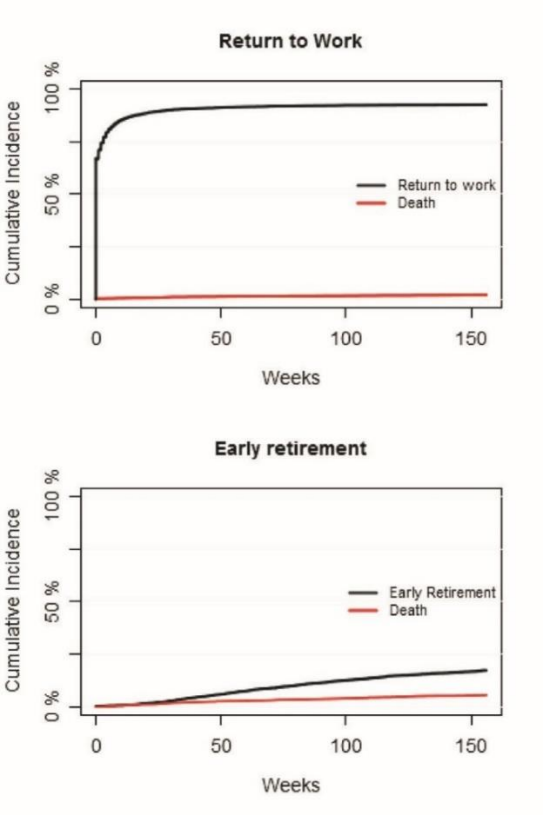

Figure 7. Cumulative incidence of return to work and early retirement with competing risk of death displayed.

Cox regression analysis of time till early retirement is displayed in figure 8. This reveals that higher age, comorbidy, dual therapy including ICS and triple therapy is associated with an increased likelyhood of early retierement. Lower age, higher educational level and SABA only use is associated with a lower risk of early retirement.

Variable	Units	N	HR(95% CI)	P-values
Sex	Male	1,513 (46.6)	0.95 (0.78-1.15)	0.6031
Age Group	35-45	455 (14.0)	0.56 (0.34-0.90)	0.0178
	46-50	544 (16.8)	1.00 (1.00-1.00)	1.0000
	51-55	1,043 (32.1)	1.57 (1.15-2.14)	0.0041
	56-59	1,203 (37.1)	1.50 (1.10-2.03)	0.0097
ISCED Level (ref 0-2)	3	1,455 (46.1)	0.85 (0.69-1.04)	0.1076
	5-6	354 (11.2)	0.80 (0.58-1.12)	0.1921
	7-8	93 (2.9)	0.38 (0.17-0.86)	0.0197
Living alone		1,040 (32.5)	1.55 (1.28-1.89)	<0.001
Comorbidity Count	1	673 (20.7)	1.26 (1.00-1.59)	0.0473
	2	204 (6.3)	1.90 (1.37-2.63)	<0.001
	3	101 (3.1)	1.68 (1.05-2.69)	0.0318
Bronchitis*		94 (2.9)	1.36 (0.86-2.16)	0.1836
Emphysema*		87 (2.7)	1.73 (1.11-2.69)	0.0146
Bronchiectasis*		23 (0.7)	0.28 (0.04-1.96)	0.1982
Cardiac Comorbidity*		272 (8.4)	1.27 (0.91-1.75)	0.1548
Diabetes*		196 (6.0)	1.15 (0.75-1.75)	0.5218
Cancer*		99 (3.1)	1.24 (0.76-2.03)	0.3922
Peripheral vascular disease/Hypertension*		86 (2.7)	0.98 (0.55-1.74)	0.9341
Anxiety*		66 (2.0)	1.34 (0.75-2.41)	0.3191
Depression*		109 (3.4)	0.99 (0.59-1.67)	0.9751
Gastro esophegal reflux*		56 (1.7)	2.01 (1.15-3.52)	0.0143
Osteoporosis*		60 (1.8)	1.77 (1.10-2.84)	0.0180
Apnea*		50 (1.5)	0.73 (0.30-1.77)	0.4839
Triple therapy		275 (8.5)	2.62 (1.98-3.47)	<0.001
LAMA + ICS or LABA + ICS		554 (17.1)	1.55 (1.19-2.01)	<0.001
LAMA + LABA		19 (0.6)	1.68 (0.62-4.57)	0.3077
LAMA or LABA		175 (5.4)	0.98 (0.62-1.55)	0.9316
ICS		401 (12.4)	1.28 (0.94-1.74)	0.1188
SABA		405 (12.5)	0.63 (0.42-0.94)	0.0237

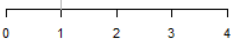

*Figure 8. Cox regression model of early retirement from the workforce. *Comorbidities and Comorbidity count was not included in the model at the same time. HR for other covariates is reported with comorbidity count in model. Hazard ratio (HR), Confidence interval (CI), cardiac comorbidity (ischemic heart disease, atrial fibrillation/flutter, and heart failure), Inhaled corticosteroids (ICS), Long-acting muscarinic antagonist (LAMA), Long acting beta2agonist (LABA), Short acting beta2agonist (SABA).*

4.1.4. FOURTH HYPOTHESIS - STUDY IV

COPD PATIENTS WITHOUT WORK HAVE MORE TREATABLE TRAITS THAN PATIENTS' PART OF THE WORKFORCE.

Study 4 includes 404 COPD patients and among these 191 were without paid work at the first-time outpatient clinic inclusion visit. The logistic regression model of the likelihood of having no paid work reveal that age, lung function, daily activity, dyspnea, fatigue score, exercise capacity, and exacerbations are associated with an increased likelihood of no paid work as shown in figure 9. Medium and higher educational level was associated with a lower likelihood of not having paid work. Including all variables in the model at the same time reveal a significant association with no paid work with higher age and exercise capacity.

Variable	Units	Median[IQR]/ Mean(sd) / N(%)	Na	OR (95%CI)	P-values
Age *	Pr. year	58 [53, 61]		1.06 (1.02–1.10)	<0.01
		58 [53, 61]		1.08 (1.02–1.14)	<0.01
Sex *	Female	211 (52.2)		1.48 (0.98–2.22)	0.060
		125 (51.4)		1.56 (0.88–2.76)	0.127
Lung function *	FEV1% predicted	55.9 (18.8)		0.98 (0.97–1.00)	<0.01
		55.6 (18.1)		1.00 (0.98–1.01)	0.612
Educational level *	Medium/High	159 (39.4)		0.62 (0.41–0.93)	0.023
	Medium/High	90 (37.0)		0.69 (0.39–1.24)	0.216
Daily activity †	Steps per day < 5000	151 (37.4)		2.36 (1.52–3.68)	<0.01
		90 (37.0)		1.59 (0.84–3.00)	0.157
Smoking status †	Active	214 (53.0)		1.37 (0.91–2.08)	0.135
		134 (55.1)		1.06 (0.60–1.88)	0.830
Dyspnea †	MRC ≥ 3	158 (42.4)	31	1.78 (1.14–2.77)	0.011
		102 (42.0)		0.93 (0.50–1.73)	0.827
Abnormal BMI †	BMI < 21 or > 30	162 (40.1)		1.32 (0.87–2.00)	0.190
		100 (41.2)		0.96 (0.54–1.69)	0.880
Fatigue score †	CIS ≥ 36	180 (58.4)	96	1.78 (1.10–2.87)	0.019
		143 (58.8)		1.43 (0.78–2.59)	0.246
Exercise capacity †	6MWD < 70%	203 (50.2)		2.62 (1.69–4.06)	<0.01
		127 (52.3)		2.29 (1.24–4.22)	<0.01
Exacerbations last year †	2 or more	103 (29.8)	58	1.80 (1.12–2.92)	0.016
		103 (29.8)		1.60 (0.86–2.95)	0.135

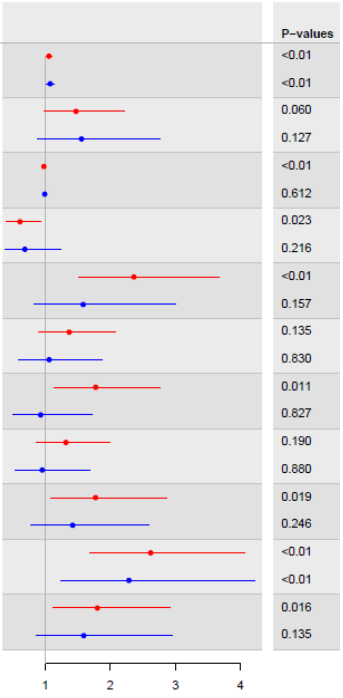

*Figure. 9 Logistic regression model exploring treatable traits related with not being in paid work. Red model: *OR of model including only confounders. Missing data for specific treatable traits are shown in Na column. †OR of treatable traits adjusted for age, sex, FEV1% and educational level. Blue model: Including all confounders * and treatable traits † in the same model. Due to missing data across different treatable traits 150 patients were excluded from blue analysis leaving 254 with complete data. Odds Ratio (OR), Confidence Interval (CI),*

standard deviation (sd), Interquartile range (IQR), Forced Expiratory Volume in one second (FEV1), Medical Research Council (MRC score), Body Mass Index (BMI), Checklist Individual Strength (CIS), 6 min walk distance (6MWD) (2).

CHAPTER 5. DISCUSSION

The following discussion section will focus on discussing the aims of the study listed in the hypothesis and aims section and will be listed accordingly.

5.1.1. EXPLORE IF WORKFORCE STATUS IS ASSOCIATED WITH READMISSION AND MORTALITY AND HEREBY IDENTIFY IF PATIENTS OUTSIDE THE WORKFORCE ARE CONSIDERED A VULNERABLE SUBGROUP OF COPD PATIENTS (STUDY I).

Consistent with previous findings, this study shows COPD patients outside the workforce have increased readmission rates and a higher mortality compared to patients who are working (38). Differences are however seen between the study by Tøttenborg et al. and *study 1* (38). Unemployed are found to have a higher one-year readmission risk then employed which was not found by Tøttenborg et al. Differences in study design may explain the differences seen. Tøttenborg et al. included voluntary early retirement and pension in the analysis which are both age dependent. The inclusion of age dependent variable makes the interpretation of workforce association with exacerbation, readmission and death difficult as they are all associated with age (83-85). S*tudy II* removes this uncertainty by including only age 35-59. Differences in inclusion time with *study II* including form AECOPD and Tottenborg et al. from outpatient visit may furthermore explain differences seen. Similar results are however seen for patients on early retirement benefit between studies. This is not surprising as the benefit is only available to patients who are significantly impaired in their working capability.

It is somewhat surprising that within this young group of patients, aged between 35-59, 12% on early retirement benefit dies within one year of their first severe AECOPD compared to seven % in patients working. This has, to this author's knowledge, not been investigated previously. For comparison, *study II* of this thesis shows the mortality rate in healthy working individuals within one year from patients 60^{th} birthday is 0.2%. These findings not only confirm that patients outside the workforce are a vulnerable population but also that having the first hospitalization due to AECOPD is a negative prognosis factor which warrants intervention.

5.1.2. EXPLORE WHICH INDIVIDUALS ARE AT RISK OF CHOOSING VOLUNTARY EARLY RETIREMENT AND IDENTIFYING POTENTIAL BENEFICIAL AND HARMFUL ASSOCIATIONS TO MORTALITY FOR INDIVIDUALS LEAVING THE WORKFORCE VOLUNTARILY (STUDY II).

Study II shows that individuals who have COPD or heart failure are more likely to choose voluntary early retirement at age 60 whereas healthy individuals are less likely. Healthy individuals were also at age 62 less likely to choose VER, however, neither the subgroup with COPD, nor the subgroup with heart failure were significantly more likely to choose VER. These findings are consistent with the existing knowledge, that the choice of voluntary early retirement both internationally and in the Danish system is associated with self-assessed health (74, 86). The changes seen in the age 62 cohort may be driven by a smaller population size. It may, however, also be an indicator of a healthy survivor bias in the study. However, a plausible explanation may also be that individuals with low educational level, COPD, and heart failure subgroups have the worst health status and therefore leave the workforce when the benefit becomes available. This will make the health bias related to the choice in these groups diminish and hereby diminish the magnitudes of effect and significance.

Voluntary early retirement in the age 60 cohort is associated with an increased mortality, which is not found in the age 62 cohort. The driver for this must be found either before or after the benefit is obtained as the status has no biological connection with health. Different studies find both beneficial and harmful effects for physical activity and mental wellbeing following retirement (59, 61, 63, 87-91). One explanation for the mortality risk seen in the age 60 cohort may be that the sum of the behavior, that voluntary early retirement enforces, is negative. This does, however, not explain why the mortality increase is not seen at age 62.

The increased mortality observed in individuals choosing voluntary early retirement at age 60 can also be explained by poor health status when the benefit is chosen. This hypothesis is supported by other studies that show those who choose voluntary early retirement are more likely to have poor health status (74, 86). This may also explain why the increased mortality risk is not seen at age 62. If individuals with the worst health status leave the workforce at age 60 by choosing voluntary early retirement, then they are removed when exploring the population form the age of 62. This creates survivorship bias in the population at age 62. This explanation of the observed mortality differences is also in line with the differences seen in the likelihood of voluntary early retirement discussed above.

The unhealthy selection bias in the age 60 and the survivorship bias in the age 62 cohort explanations fits well with the voluntary early retirement likelihood estimates

in the COPD subgroup. Disease severity in COPD patients has previously been found to associate with poor workforce connection (70, 92). It is therefore likely that the more severe COPD patients leave the workforce at age 60 and the less severe wait until age 62. It is however interesting that the increased likelihood is observed in the healthy group also. This group however have a lower mortality rate therefore the absolute risk is lower in this group. The choice of voluntary early retirement, also in patients without chronic diseases, is associated with patients perceived health, which supports these findings (74). The odds ratio likelihood estimates across the different groups are however similar with the highest mortality likelihood estimates seen in the COPD subgroup in both the age 60 and age 62 cohort.

Study II contributes with a potential explanation of the diverging results seen in voluntary early retirement studies. At the same time, no beneficial effects found. It is confirmed in the study that the choice of leaving the workforce is associated with health status and that the choice comes with an increased mortality risk. The study also shows that the increased mortality is associated with the time of voluntary retirement. The likely explanation for this is an unhealthy selection bias if voluntary early retirement is chosen when it becomes available at age 60.

5.1.3. CHARACTERIZE PATIENTS AT RISK OF DELAYED RETURN TO WORK AND PERMANENT DETACHMENT (STUDY III).

Study III shows that the majority of patients return to work quickly following severe AECOPD. No studies previously explored return to work following severe AECOPD to the best of my knowledge (93). A relatively high percentage of the COPD patients that do not return to work receive early retirement during follow-up. This may indicate that admission for AECOPD initiate the detachment. Early retirement is not granted easily in the Danish social system and efforts are in place to retain individual's workforce connection. This may explain that the drop off due to early retirement has no peak from the first AECOPD as the process of being awarded early retirement is long. Studies predicting early retirement using a follow-up design are to the best of my knowledge not available. One explanation for this may be that to be able to include a relevant sample size and have sufficient follow-up until the early retirement event would require considerable resources in a clinical setting. The use of registry data over a 15-year time period makes this possible with inclusion of a relevant sample size at first admission to the hospital.

Study III identifies higher age, more comorbidity and lower education as predisposing factors of early retirement. These factors are known risk factors of early retirement in general and therefore not surprisingly also for COPD patients (94, 95). *Study III* also shows that living alone is associated with early retirement inconsistent with previous

findings showing that marital status was not associated with disability pension (94). The reason for the discrepancies may be that marital status does not account sufficiently for individuals living together out of marriage. The association seen with higher treatment step is likely an indicator of disease severity more than a harmful effect in general. This is supported by the findings that disease severity in COPD patients is associated with workforce connection (70, 92).

There are multiple reasons to try to avoid patients becoming early retirement recipients. Early retirements' association with higher readmissions and mortality rates, as found in *study II*, may indicate that if the event can be avoided readmission and mortality rates may improve. Early retirement may furthermore represent an event which, from an societal perspective, is important to avoid, to limit the public expenses (96). Early retirement also likely indicates a functional decline with the benefit only available to those who are not able to work. Intervention aimed at improving patients' workforce connection may therefor prove valuable in improving multiple patient outcomes.

Noteworthy is the magnitude of patients excluded from the study (70%) due to detachment from the workforce at the time of first admission with AECOPD. The frequency is higher than the rate of around 60% which has been seen in other studies (42-44). A hypothetical explanation is that those admitted to the hospital due to AECOPD at this young age have relatively severe COPD compared to age-matched COPD patients in general. Early identification and intervention aimed at maintaining COPD patients' workforce connection must therefore be initiated before first admission with AECOPD if improvements are to be made.

5.1.4. EXPLORE POTENTIAL AREAS WHERE INTERVENTION MAY IMPROVE PATIENTS OUTSIDE THE WORKFORCE (STUDY IV).

In *study IV* COPD patients with lower educational level and/or higher age have a higher likelihood of being without paid work. These findings are consistent with the findings regarding early retirement in *study III* and the findings in studies exploring risk factors of disability pension (94, 95). Unfortunately, the study was conducted without differentiating the cause of not having paid work and some of the included patients may therefore be unemployed and searching for work.

COPD patients without paid work have more treatable traits than COPD patients with paid work, among these exercise capacity and physical activity which is consistent with previous findings in the general population (66). In addition, the study shows that lung capacity is associated with an increased likelihood of being without paid work which is consistent with other studies (97).

As the study is cross sectional causality cannot be determined. The existing knowledge on workforce connection may, however, indicate that the functional decline precedes the detachment from the workforce. A study by Böckerman et al. examined the longitudinal association between self-assessed health status and detachment from the workforce has been explored (57). This study found that self-assessed health status does not change in relation to unemployment and that patients with lower perceived health statues are more likely to become unemployed (57). This is not the same as the treatable traits that we have explored in study IV, however, it is likely that self-assessed health status will be lower in patients with more treatable traits.

Study IV confirms that being outside the workforce for COPD patients is linked to having more treatable traits. This information contributes to *Study I*, *II* and *III* by the indication that patients with a workforce status without paid work are likely to be more burdened by treatable traits, hereby making intervention possible.

CHAPTER 6. STRENGTHS AND LIMITATIONS

The Danish national registry studies (study 1, 2, and 3) utilize nationwide data which makes inclusion of many individuals possible (75). The use of the CPR number as an identifier across the multiple different registries eliminates some selection bias in that the individuals included were not aware of any analysis being performed. The use of the Danish registries is therefore exceptional to explore real world tendencies.

The choice to include patients in study 1 and 3 from the age of 35 was done to avoid excluding patients diagnosed at younger age. This decision is somewhat controversial in that the age limit is low for a COPD population however some patients receive their diagnosis from this age (6-9, 98). An exclusion of these patients would thereby make the result less applicable in the general COPD population.

The use of first AECOPD as inclusion time in study 1 and 3 are meaningful from a clinical perspective as it is an identifiable timepoint for COPD patients. It does, however, come with some uncertainties. The accuracy of a part of the criteria used has been validated by Thomsen et al, who found a positive predictive value of 92% and that 19% of patients admitted with acute respiratory failure or pneumonia had underlying COPD (80). The positive predictive value is from a registry perspective very good. Further exclusion criteria are however added in our studies including exclusion of DJ448B (asthmatic bronchitis) and patients with a previous asthma diagnosis. The validation study does however not report the reasons for miscoding of patients, and it is therefore not possible to tell if the exclusions would improve the positive predictive value. The patients with acute respiratory failure or pneumonia who were not correctly characterized as COPD patients creates the possibility that some patients may have been admitted with AECOPD prior to the "First time AECOPD hospitalization" that is recorded in study 1 and 3. This uncertainty in the data is not expected to influence the interpretation of the prediction models used, but it may however underestimate the number of patients with a first-time admission and affect the characteristics of patients at the time of inclusion due to prior hospital contact.

As for all epidemiologic studies, the causal effects in the studies are uncertain as discussed previously.

The reason for study 1 and 3 to explore workforce connection only in patients below 60 is the existence of voluntary early retirement in the Danish social system. With a

benefit that is dependent on the age of individuals in the study population an inclusion of the variable would potentially skew the results as the variable would share risk with an age 60-64 group. In study 1 the population explored would approximately double it we had included patients with their first AECOPD in this interval making the potential issues in including this group large (see appendix C).

CHAPTER 7. CONCLUSSION

IDENTIFY VULNERABLE COPD PATIENTS AND PATIENTS AT RISK OF BECOMING VULNERABLE USING WORKFORCE CONNECTION (THESIS AIM).

The thesis confirms that COPD patients have a poor connection to the workforce with early retirement and early voluntary retirement as poor prognostic indicators regarding mortality. Patients at risk of retiring early are patients with more comorbidity, lower socioeconomic status, and higher age. COPD patients outside the workforce have more treatable traits which may suggest that interventions aimed at improving patients' physical performance and hereby possibly workforce connection may be possible through pulmonary rehabilitation. If workforce connection cannot be improved, the prognostic value of workforce connection should still guide clinicians in identifying vulnerable patients. Studies are needed to explore whether workforce retention and improvement in patient outcomes is possible by using the prognostic indicators found in this thesis.

CHAPTER 8. PERSPECTIVES

The economic benefits of maintaining COPD patients' workforce connection from a societal perspective are obvious. The high occurrence of early retirement, sick leave and unemployment rates observed in *study I, III and IV* comes with increased public spending on social benefits and lost tax revenue. If workforce connection can be improved, social benefits may be reduced, and tax revenues may increase which may finance any interventions necessary.

Study III shows that for some, AECOPD precedes the detachment from the workforce. At study inclusion 70% were excluded because they were not in paid work at the beginning of the study raises. This raises the question for how may among those already outside the workforce does COPD precede the detachment from the workforce. This was explored in an abstract accepted to the ERS 2021 (appendix D). Among those permanently detached from the workforce, 57% had redeemed a prescription on inhalation medication prior to their permanent detachment from the workforce (appendix D). The average time from first prescription to permanent detachment in patients with a prescription prior to detachment is on average four year. These findings show that intervention is possible for many COPD patients prior to their detachment from the workforce. This makes it likely that early interventions aimed at workforce retention is possible. It is however clear that patients must be identified in the primary sector or in an out-patient setting with 76% outside of the workforce at first admission with AECOPD in patients between 35-64 years old (see appendix C). Future studies should explore whether interventions towards the at-risk COPD groups characterized in *study III* may help avoid detachment from the workforce and in addition whether this improves patient outcomes, such as quality of life, physical activity and mortality. The treatable traits explored in study IV indicate that pulmonary rehabilitation may be a relevant intervention to explore. Interventions aimed at improving workforce connection should be evaluated in a cost efficiency setting as it is possible that interventions may be cost efficient if workforce retention is possible.

The prognostic value of workforce connection in both *study I* and *II* identifies COPD patients outside the workforce as vulnerable. Future studies should explore whether reestablishing workforce connection is possible with interventions. Even if improving workforce connection is not possible interventions is still needed to improve the vulnerable COPD patients' survival.

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APPENDICES

Appendix A. Workforce connection coding in DREAM

Codes from DREAM database and which are treated as part of workforce and which are considered permanent detachment. Codes are from DREAM version 39.

Working	**Unemployed**
“” = part of the workforce	“111-114 or 130-140 or 143-149” or “151-153” or “211-218” or “231” or “299” “720-739” = unemployment benefit
“121-123” = holiday benefits	“124-126” = vacation benefit for unemployed
“412” = Leave of absence	“700-719” unemployment benefit for immigrants
“413” = Educational leave of absence	”750-768” Revalidation benefit
“511” = service job	**Sick Leave**
“521” = Adult apprentice	“810-818 or 870-878” = workforce ability benefit
“522” = Rotation substitute	890-899” = sick leave
“651-652” = State educational support	**Early retirement**
“661” = Adult state educational support	“740-748 or 771 or 774” = “Flex Job”
“881” = Maternity leave	“781” = Sheltered job
	“783” = Early retirement

BENEFIT DESCRIPTIONS:

Holiday benefits = payment received during holiday while currently employed; leave of absence = Leave of absence from the workforce, Educational leave of absence = leave of absence from education system; “Service job, adult apprentice and rotation substitute = support requires employment; “State educational support and adult state educational support = payment received while studying; maternity leave = public support during maternity leave; Flex Job = benefit available to people with greatly impaired working ability who have work at greatly reduced time; sheltered job = only available to people receiving early retirement; unemployment benefit = benefit available to unemployed; vacation benefit unemployed = benefit available during vacation during unemployment; unemployment benefit for immigrants = unemployment benefit available to not Danish nationals; revalidation benefit = benefit available while being evaluated for potential reschooling with the prospect of full or partial return to work; workforce ability benefit= benefit requiring inability to work due to illness when being evaluated for work ability.

Appendix B. Comorbidity definitions

ICD-10 codes and ACT codes used to define comorbidity

DIAGNOSIS CODES	ICD-10 codes	Medication (ATC-code)
AMI	I21-I23, I252	
Ischemic heart disease	I20, I21, I23-25,	
Cardiac insufficiency	I42 (excluding I428B), I43, I50, I099, I110, I130, I132, I255	
Atrial fibrillation/flutter	I48	
Peripheral vascular disease	E105, E115, E125, E135, E145, I70-I72, "I731", "I738", "I739", I74, I77, I790, I792, K551, K558, K559, Z958, Z959	
Cerebrovascular disease	I60-I69, G45, G46, H340	
Dementia	F00-F03, G30, F051, G311	
Chronic pulmonary disease (excluding COPD)	J40-J43, J45-J47, J60-J67, J84, I278, I279, J684, J701, J703, J704, J920, J953, J961, J982, J983	
Pulmonary fibrosis	J84, J631, J633, J635, J628A, J638A, J638B, J701, J703	
Bronchitis	J42	
Emphysema	J43, J982, J983	
Bronchiectasis	J47	
Rheumatic disease	M05, M06, M08, M09, M30-M36, D86	
Peptic ulcers	K25-K28, K221	
Mild liver disease	K700-K703, K713-K715, K762-K764, K73, K74, B18, K709, K717, K760, K769	

Severe liver disease	B150, B160, B162, B190, I850, I859, I864, I982, K704, K711, K721, K729, K765-K767	
Liver cirrhosis	K703, K717, K74	
Diabetes without comp	E100, E101, E109, E110, E111, E119, E120, E121, E129, E130, E131, E139, E140, E141, E149	A10
Diabetes with comp	E102-E108, E112-E118, E122-128, E132-E138, E142-E148	
Hemiplegia/paraplegia	G801, G802, G830-G834, G81-G82, G041, G114, G839	
Chronic renal failure	N032-N037, N052-N057, Z490-Z492, N18, N19, N26, I120, I131, I132, N250, Z940, Z992	
Cancer without metastasis + lymphoma + leukaemia	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	
Pulmonary cancer	C34, C398, C399	
Pancreatic cancer	C25	
Oesophageal cancer	C15	
Mamma cancer	C50	
Cancer with metastasis	C77-C80	
AIDS/HIV	B20 – B24	
Anxiety	F41	N05B
Depression	F32	N06A
Gastro oesophageal reflux	K21	
Sleep apnoea	G473	
Osteoporosis	M80, M81, M82	
Hypertension		C02, C03, C07, C08, C09

Appendix C. ERS-abstract 2021

Title: Workforce connection at first admission with AECOPD and age at permanent detachment

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Introduction: Many patients with chronic obstructive pulmonary disease (COPD) experience early retirement. Understanding the magnitude of COPD patients outside the workforce, and when permanent detachment (PD) from the workforce takes place may facilitate interventions aimed at retaining workforce connection.

Aims: To examine workforce connection of patients admitted with acute exacerbation of COPD (AECOPD) for the first time and exploring the median age at PD.

Method: This nationwide retrospective cohort study, based on Danish registry data, included patients 35-64 years at first admission with AECOPD between 1999-2015, excluding patients with a previous asthma diagnosis. Workforce connection was divided into working, unemployment benefit, sick leave, early retirement, and early voluntary retirement (Danish voluntary detachment benefit available from the age of 60). Early retirement and early voluntary retirement were treated as PD. Two age estimates at PD were calculated, one including patients receiving PD benefits at the time of the work registry's beginning in 1993 and one excluding these patients.

Results: The study included 22,499 patients with 5,457 (24%) working, 1,844 (8%) on unemployment benefit, 1,135 (5%) on sick leave, 11,711 (52%) on early retirement and 2,352 (11%) on early voluntary retirement (table 1). PD was seen in 62.5% (14,063/22,499). Median age at PD was 50 years interquartile range (44-57 years) and when excluding patients receiving PD benefits at the beginning of the registry (N = 10,260) the average age was 53 years (46-60). Early voluntary retirement benefit becomes available from the age of 60 which explains the high increase in figure 1.

Conclusion: At first admission 63% received PD benefits. The median age at PD in patients with accurate date of PD was 53 years. Early intervention is needed to avoid PD.

Appendix D. ERS-abstract 2021

Title: Treatment for chronic obstructive pulmonary disease prior to early permanent detachment from the workforce

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Introduction: Chronic obstructive pulmonary disease (COPD) patients are vulnerable to early retirement from the workforce. If intervention is possible in COPD patents to improve patient's workforce connection depends on the diagnosis preceding early retirement.

Aims: The aim is to investigate whether COPD patients have received treatment for COPD prior to detachment from the workforce and how long they were treated before leaving the workforce.

Method: This nationwide Danish epidemiologic study includes patients, 35-64 years old, at the time of first admission to the hospital with an exacerbation of COPD between 1999 to 2015. Registry data on prescriptions were available from 1995. Patients with detachment prior to 1996 were therefore excluded. Patients receiving early retirement (including early retirement and early voluntary retirement benefit (available from the age of 60)) at first admission were included in the study. Date of first early retirement benefit and first prescription of inhaled airway medication (INHA) (long or short acting adrenergic agonists, long or short acting anticholinergic and inhaled corticosteroids) were registered. Time from first prescription to detachment was calculated in patients receiving airway medication prior to detachment.

Results: A total of 8,392 COPD patients, 52% females, were included in the study. The median age was 60 years at first admission. A total of 4,795(57%) had received (INHA) before early retirement, with a median time from first prescription to early retirement of 1,529 days, interquartile range (679–2.806 days) (see table 1 and figure 1).

Conclusion: Half of COPD patients received INHA with a median time of first prescription more than four years before detachment from the workforce. Early actions to maintain COPD patients' workforce connection including treatment optimization should be considered.

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