OCCUPATIONAL EXPOSURE

AND COPD

A DANISH POPULATION-BASED STUDY

PhD thesis

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ORIGINAL PAPERS

The thesis is based on the following original research papers:

Paper I — Occupational chronic obstructive pulmonary disease in a Danish population-based study

Accepted paper included as Appendix E, page 93:
Würtz et al. COPD. 2014 Nov 21. [Epub ahead of print]

Paper II — Occupational chronic obstructive pulmonary disease among Danish women: a population-based cross-sectional study

Submitted manuscript in review for publication in BMC Women's Health, MS: 8445796661393067, included as Appendix F, page 109.

Paper III — Occupational COPD among Danish never smokers – a population-based study

Submitted manuscript in review after second revision for publication in Occupational and Environmental Medicine, Manuscript ID oemed-2014-102589, included as Appendix G, page 127.

Paper IV — Occupational exposure increases the four-year incidence of COPD among 45-84-year old Danes

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PREFACE

My engagement in occupational COPD was initiated by Øyvind Omland. I submitted an application as research assistant in his review project regarding occupational COPD. I was late for the job interview, but he luckily believed in my skills as a Master of Health Science. I think I caught up well on the untimely start and have thus ended up writing this thesis. With a prior career as biomedical laboratory scientist in cytology this was not straight forward, but thank you Øyvind, that you believed in me and have supported me all the way – although I am not a physician! I have learned a lot and I appreciate working within the field of medical research.

The last three years have been a long journey with many different tasks in relation to the PhD assignment. I have a lot of people I wish to thank for their help, understanding and support during the process:

- My co-supervisors Tine Halsen Malling for giving a wonderful daily support and always being understanding, Vivi Schlünssen for giving great methodological response and encouragement, Jens Georg Hansen for having great knowledge and facts about the data set, and Charlotte Brasch-Andersen being essential for the ongoing genetic part of my study.
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ENGLISH SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is a common disease affecting morbidity, disability and mortality all over the world and is characterised by airflow limitation due to the chronic inflammation. In populations aged above 40 the prevalence is about 10% and higher among men than among women. The main risk factor for COPD is smoking, although only a fraction of approximately 25% of continues smokers develop COPD. Nevertheless, about 80% of COPD cases could be attributed smoking.

Among other risk factors are occupational exposures in which vapour, gas, dust, and/or fume (VGDF) can induce chronic inflammation similar to effects seen from particles inhaled by smoking. The population attributable fractions (PAF) of occupational COPD are about 15% of the COPD cases.

The thesis aim to address the association between COPD and occupational exposure in a population-based cohort of Danes aged 45-84-years (Paper I-IV).

The population included 1626 women and 3091 men (N=4717) and baseline data were assessed in 2004/2006 while follow-up data (N=2624) were assessed in 2008/2010 and each time recruited through their general practitioner. Data were based on lung function measurements and questionnaires. COPD was defined by lung function measurements according to the method of Lower Limit of Normal (LLN).

A priori the Danish version of the International Standard Classification of Occupations, revision 1988 (DISCO-88) were used to select jobs with known presence of occupational exposure. The self-reported jobs with occupational exposure were then restricted to those included among the selected DISCO-88 codes. The cumulated occupational exposure was expressed as duration of exposed jobs. The main occupational exposure was organic dust (primarily agriculture) while 49% reported no lifetime occupational exposure.

Paper I included the whole baseline study population with 279 COPD cases and found an age-standardised prevalence of COPD at 5.0% (95% CI: 5.0;5.0) significant lower in women compared to men, 4.6% (95% CI: 4.6;4.6) and 5.0% (95% CI: 5.0;5.0), respectively. The adjusted odds ratio (ORadj) from the mixed model regression analysis, for medium (5-14 years) VGDF exposure was 1.61 (95% CI: 1.03;2.51), while the ORajd for high (≥15 years) organic dust exposure was 1.56 (95% CI: 1.09;2.24). Significant trends in exposure level were also present in these associations, p=0.031 and p=0.017, respectively.

Paper II included the women (N=1626) from the baseline study population. In all 279 women were assigned a relevant occupational exposure while 76 had COPD. The occupational exposures were dichotomised as never or ever occupational exposed. The mixed model regression analyses revealed occupational exposure to be asscociated to COPD, ORadj if exposed to VGDF and organic dust, 1.98 (95% CI: 1.06;3.69) and 2.05 (95% CI: 1.04;4.08), respectively. The PAF were estimated to be 14% and 15%, respectively.

Paper III included the never smokers (N=1575) from the baseline study population. Occupational exposure were present in 658 (42%) of the never smokers and 26 had COPD equal to a prevalence of 1.7%. The occupational exposures were dichotomised as never or ever occupational exposed. In the mixed regression model never smokers exposed to VGDF and organic dust had an increased occurrence of COPD, ORadj 3.69 (95% CI: 1.36;10.04) and 2.94 (95% CI: 1.05;8.22), respectively. The study PAF for COPD among never smokers caused by occupational exposure was 48% (95% CI: 30;65) for VGDF exposure and 41% (95% CI: 19;62) for organic dust exposure.

Paper IV was focusing on COPD incidence and annual decline in lung function in the four-year follow-up study. COPD cases at baseline were excluded (n=120) thus 2624 very eligible for analysis. The overall annual mean (±SD) change in lung function in men was ΔFEV_1 -50 mL/yr (±94) and ΔFVC -58 mL/yr (±133) and in women -31 mL/yr (±69) and -38 mL/yr (±105), respectively. No analyses of annual decline in lung function in relation to occupational exposures reach statistical significance. New-onset COPD was identified in 38 subjects and the age-standardised incidence was 0.9% (95% CI: 0.9;0.9) (men 1.0% (95% CI: 1.0;1.0), women 0.7% (95% CI: 0.7;0.7)). The adjusted incidence rate ratios (IRR) from the mixed regression analyses on occupational exposures were associated with COPD; low (<5 years) VGDF exposure 3.71 (95% CI: 1.17;11.8), high VGDF exposure 2.62 (95% CI: 1.06;6.48), low organic dust exposure 3.24 (95% CI: 1.07;9.83), but with no clear exposure-response relation.

The results from this thesis suggest occupational exposures to be associated to COPD. COPD was associated to occupational exposure also in never smokers and women. We found exposure-response relation in the cross sectional analyses, but not supported in the longitudinal analyses. The VGDF exposure consisted predominantly of organic dust. The results are in accordance with other international studies. However, the estimated PAFs were higher among never smokers compared to earlier studies, while to our knowledge, no comparable PAF previously have been established among women. The longitudinal analyses indicate an association between occupational exposure and incident COPD despite the short follow-up time.

The present study emphasise the major influence that exposures from occupation as VGDF and organic dust have on COPD, also among never smokers and women. These findings from the labour market in Denmark might indicate that even low exposures from work over time can have an impact on the development of COPD. The awareness by recognising these data ought to be transformed to preventive efforts to eliminate occupational COPD and thus improve public health.

DANSK RESUMÉ

Kronisk Obstruktiv Lungesygdom (KOL) er en udbredt sygdom der påvirker morbiditet, invaliditeten og mortaliteten over hele verden. KOL er karakteriseret ved en nedsat lungefunktion på grund af en kronisk inflammation i lungerne. Prævalensen er ca. 10 % hos befolkningen over 40 år, og er højere blandt mænd end blandt kvinder. Den væsentligste risikofaktor for KOL er rygning, selvom kun ca. 25 % af rygere får KOL. Alligevel kan rygning kun forklare optil ca. 80 % af KOL tilfældene.

En anden risikofaktor er erhvervsmæssig eksponering for damp, gas, støv og/eller røg (VGDF) der ved KOL foranlediger en kronisk inflammation med tilsvarende effekt som partiklerne der inhaleres ved rygning. Den andel af KOL der kan undgås hvis den erhvervsmæssige eksponering fjernes er ca. 15 % (the population attributable fraction (PAF)).

Formålet med denne afhandling er at se på associationer mellem KOL og erhvervsmæssige eksponeringer i en kohorte af den danske befolkning i alderen 45-84 år (Artikel I-IV).

Baseline data blev indsamlet i 2004/2006 og kohorten inkluderede 1626 kvinder og 3091 mænd (N=4717), mens de longitudinelle data (N=2624) blev indsamlet i 2008/2010, begge gange via deres egen praktiserende læge. Data var baseret på lungefunktionsmålinger og spørgeskemaer. KOL blev defineret ud fra lungefunktionsmålingerne og den nedre normale referencegrænse (Lower Limit of Normal (LLN)).

A priori blev der udvalgt job koder med kendt erhvervsmæssige eksponeringer ud fra den danske version af 'The International Standard Classification of Occupations, revision 1988' (DISCO-88). De selvrapporterede job med en erhvervsmæssig eksponering blev efterfølgende afgrænset til de a priori udvalgte DISCO-88 koder. Den mest udbredte erhvervsmæssige eksponering var organisk støv (primært landbrug) mens 49 % ikke rapporterede nogen form for erhvervsmæssig eksponering i deres arbejdsliv.

Artikel I inkluderede hele baseline kohorten med 279 KOL tilfælde. Den aldersstandardiserede prævalens af KOL var 5,0 % (95 % CI: 5,0;5,0) og signifikant lavere blandt kvinder 4,6 % (95 % CI: 4,6;4,6) sammenlignet med mænd 5,0 % (95 % CI: 5,0;5,0). Den justerede odds ratio (ORadj) fra den mixed model regressionsanalyse var for en medium (5-14 år) VGDF eksponering 1,61 (95 % CI: 1,03;2,51), og for høj (≥15 år) organisk støv eksponering ORadj 1,56 (95 % CI:

1,09;2,24). Eksponeringsniveauerne afspejlede yderligere signifikante tendenser i disse eksponeringer, henholdsvis p=0,031 og p=0,017.

Artikel II inkluderede kvinderne (N=1626) fra baseline kohorten. I alt havde 279 kvinder en relevant erhvervsmæssig eksponering og 76 kvinder havde KOL. Den erhvervsmæssige eksponering blev dikotomiseret til, om kvinderne havde haft en erhvervsmæssig eksponering eller ej. Den mixed model regressionsanalyse viste en øget association med KOL for VGDF og organisk støv eksponering med henholdsvis ORadj 1,98 (95 % CI: 1,06;3,69) og 2,05 (95 % CI: 1,04;4,08). Ved de to eksponeringer blev PAF henholdsvis estimeret til at være 14 % og 15 %.

Artikel III inkluderede ikkerygerne (N=1575) fra baseline kohorten. Blandt ikkerygerne havde 658 (42 %) en erhvervsmæssig eksponering og 26 havde KOL svarende til en prævalens på 1,7 %. Den erhvervsmæssige eksponering blev dikotomiseret til, om ikkerygerne havde haft en erhvervsmæssig eksponering eller ej. I den mixed model regressionsanalyse havde ikkerygerne eksponeret for VGDF og organisk støv en øget association med KOL med henholdsvis ORadj 3,69 (95 % CI: 1,36;10,04) og 2,94 (95 % CI: 1,05;8,22). PAF for KOL blandt ikkerygere forårsaget af en erhvervsmæssig eksponering var 48 % (95 % CI: 30;65) for VGDF og 41 % (95 % CI: 19;62) for organisk støv.

Artikel IV fokuserede på den fire-årige incidens af KOL, samt det årlige fald i lungefunktionen i det longitudinelle studie. De der havde KOL ved baseline blev ekskluderet (n=120) så 2624 blev inkluderet i studiet. Den årlige gennemsnitlige (± standardafvigelse (SD)) ændring i lungefunktionen blandt mænd var ΔFEV_1 -50 ml/år (±94) og ΔFVC -58 ml/år (±133), og for kvinderne var det henholdsvis -31 ml/år (±69) og -38 ml/år (±105). Analyserne af det årlige fald i lungefunktionen var ikke statistisk signifikante. Incident KOL blev identificeret hos 38 deltagere, og den aldersstandardiserede incidens var 0,9 % (95 % CI: 0,9;0,9) (mænd 1,0 % (95 % CI: 1,0;1,0), kvinder 0,7 % (95 % CI: 0,7;0,7)). Fra den mixed model regressionsanalyse var den justerede incidens rate ratio (IRR) for erhvervsmæssig eksponering associeret med KOL; lav (<5 år) VGDF eksponering 3,71 (95 % CI: 1,17;11,8), høj VGDF eksponering 2,62 (95 % CI: 1,06;6,48), lav organisk støv eksponering 3,24 (95 % CI: 1,07;9,83), dog uden klare eksponerings-respons sammenhænge.

Resultaterne fra artiklerne inkluderet i denne afhandling indikerer at en erhvervsmæssig eksponering er associeret med KOL. KOL var ligeledes associeret til den erhvervsmæssige eksponering blandt ikkerygere og kvinder. Vi fandt eksponerings-respons relationer i tværsnitsstudierne, der dog ikke blev understøttet i de longitudinelle analyser. VGDF eksponeringen bestod overvejende af organisk støv. Resultaterne er i overensstemmelse med andre internationale studier. Imidlertid var de estimerede PAF højere blandt ikkerygere sammenlignet med andre studier, hvorimod vi ikke har kendskab til andre sammenlignelige estimater af PAF

blandt kvinder. På trods af den korte opfølgnings tid påviste de longitudinelle analyser en association imellem erhvervsmæssig eksponering og incident KOL.

Dette studie understreger den store indflydelse erhvervsmæssig eksponering for VGDF og organisk støv har på KOL, også blandt ikkerygere og kvinder. Disse fund fra det danske arbejdsmarked, kunne indikere at selv lave erhvervseksponeringer kan have betydning for udviklingen af KOL. Bevidstheden om disse resultater bør resultere i et forebyggende arbejde for at eliminere den erhvervsmæssige KOL og generelt forbedre folkesundheden.

ABBREVIATIONS

ATS	American Thoracic Society
CI	Confidence Interval
CNV	Copy Number Variation
COPD	Chronic Obstructive Pulmonary Disease
CPR	Danish Civil Registration
DALY	Disability-Adjusted Life Years
DISCO-88	Danish edition of the International Standard Classification of Occupations – edition 1988
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in the first second of expiration
FVC	Forced Vital Capacity
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	General Practitioners Practice
GWAS	Genome-Wide Association Study
IRR	Incidence Rate Ratio
ISCO-88	International Standard Classification of Occupations – edition 1988
ISCO-88 (COM)	The European Union version of ISCO-88
LLN	Lower Limit of Normal
N	Number included
NCPS	The North Jutland COPD Prevention Study
OR	Odds Ratio
ORadj	Adjusted Odds Ratio
PAF	Population Attributable Fraction
qPCR	Quantitative Polymerase Chain Reaction
ROS	Reactive Oxygen Species
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
VGDF	Vapour, Gas, Dust and Fume

1. INTRODUCTION

1.1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) in these phrases:

> 'Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases' (1).

This description emphasises the high prevalence of COPD. The latest Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) from 2010 globally rank COPD as 3rd in causes of age-standardised deaths only exceeded by ischemic heart disease and stroke, Figure 1.1 (2). Thus, passing the 2030 projected 4th mortality rank from 2006 (3). The burden of COPD is not restricted to mortality moreover disability is of major concern in COPD. Estimates from GBD rank Disability-Adjusted Life Years (DALY) quantifying the burden of disease from combined mortality and morbidity as well (4). In 2010 COPD by DALY was ranked as 11th in Western Europe and as 4th in Denmark (globally 7th). In Denmark DALY caused by COPD rank above e.g. lung cancer, stroke and road injury (5). Furthermore, COPD patients have a wide range of co-morbidities as e.g. cardiovascular diseases, osteoporosis, depression and lung cancer (1).

The economic costs caused by COPD have additional consequences for the society and the patients, as well as their spouses consisting of health-related contacts, medication use and higher socioeconomic related costs (6,7).

The most important tool to assess COPD is evaluating the lung function by spirometry. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have collectively published an updated standardisation of spirometry (8). The individual airflow depends on sex, age, height and ethnicity and is compared to a normal reference population. During lifetime a normal lung function development is described by periods of growth (approx 18-20 yr), plateau (approx 20-35 yr) and decline as a trait of normal ageing (9). In theory, all three phases could be affected by exposures and implications for COPD development by decreased peak, shortened plateau or accelerated decline, respectively (10).

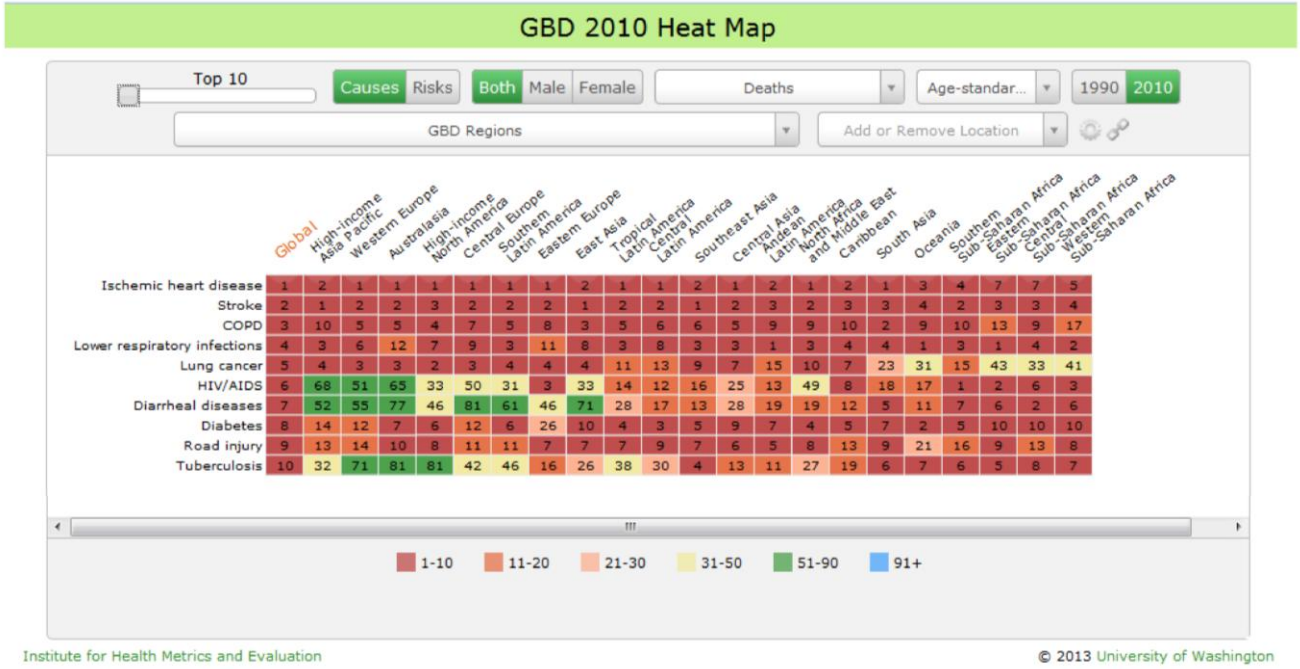

Figure 1.1: The Global Burden of Disease Heat Map (screenshot), The Institute for Health Metrics and Evaluation, University of Washington (5), presents the top 10 rank of age-standardised deaths in 2010 by regions.

COPD is characterised by heterogeneous phenotypes in respect of the clinical presentation, physiology, imaging, response to therapy, decline in lung function and survival with diverse degree of disease progression (11,12).

Although COPD is a global disease there are differences in prevalence among gender and countries. The BOLD study summarised the COPD variation from population based studies from 12 cities across the world among subjects aged ≥40 years. The overall moderate COPD prevalence was 10.1% and varied along with city and gender. Men had a higher prevalence 11.8% (range: 8.5-22.2) compared to women 8.5% (range: 5.1-16.7) (13). Moreover, currently available treatments have minimal impact on progression of the disease (10).

1.2. ETIOLOGY AND PATHOGENESIS FOR COPD

COPD is a common and complex disease. Exposure to particles is the major risk factor for COPD and mainly considered as smoking, which is the most important causal factor for COPD development (10,14). Up to 25% of continues smokers develop COPD (15) and smoking is estimated to account for ≤80% of COPD cases (16). Nevertheless, other estimates report that worldwide up to half of COPD cases are due to non-smoking causes e.g.: exposure to biomass smoke; occupational exposure to vapour, gases, dust and fumes (VGDF); history of pulmonary tuberculosis or chronic asthma; outdoor air pollution; diet; genes; age; gender; lung growth; passive smoking; poor socioeconomic status and early life events (1,10,14,17,18). Time periods of exposures presumed to affect the normal lung function throughout the whole life-span is for example with genetics, air pollution, and passive smoke potential impairments, whereas personal smoking and occupational exposures begin later in life, as described and illustrated by Eisner (10). Although COPD is a disease primarily diagnosed at older ages, its origin might be present before birth by prenatal effects and in early childhood (18).

COPD is characterised by airflow limitation due to chronic inflammation in the airways, composed in three major clinical phenotypes: emphysema, chronic bronchitis and small airways disease (18,19). Although an approach towards multi-dimensional phenotyping (information from different scales: e.g. organ-person, tissue-organ, cell-tissue, gene-cell) is forthcoming to improve COPD outcome and move towards personalised medicine (20). A phenotype could be described as any observable characteristics that results from gene-environment interactions (20). Despite the chronic inflammation recognised in COPD, there is sparse knowledge about a possibly normal lower respiratory tract microbiota, maybe dysbiosis is a triggering event for COPD or a biomarker of more severe disease (21). Nevertheless, the microbiome in different parts of the COPD affected lung and at different COPD stages seems to be heterogeneous (21).

The immune response in COPD is disturbed with excess accumulation of neutrophils and macrophages in the lungs, unleashing a cocktail of proteolytic enzymes leading to uncontrolled tissue destruction (19). The cellular responses to environmental stressors are controlled by reactive oxygen species (ROS), which include free radicals (superoxide radical anion, nitric oxide, radical hydroxyl, etc.) and non-free radical reactive species (H_2O_2, hypohalides, peroxynitrite, ozone, etc.) and produce oxidative modification of biomolecules (22). There is evidence for an increased generation of ROS expressed as oxidative stress in COPD patients (23).

The exact pathways leading to COPD are unknown and one pathway alone will apparently not fully explain the COPD pathophysiology. The four main hypotheses are the protease-antiprotease hypothesis, the British hypothesis, the autoimmunity hypothesis, and the Dutch hypothesis (19).

Briefly described the protease-antiprotease hypothesis is that proteases break down the connective tissue (elastin) in the lung to induce emphysema as a description of the lung changes e.g. induced by deficiency of α-antitrypsin inhibitors in the serine proteases. In normal lungs the proteolytic activities are counteracted by antiproteases in the lung (19) and the importance of protease-antiprotease balance in the pathogenesis of emphysema is strengthen in a candidate gene study among Finnish construction workers (24).

The British hypothesis for COPD is explained by recurrent bronchial infections, also often seen in exacerbation. The chronic and progressive path of COPD is often aggravated by exacerbations as additional acute inflammation defined by GOLD as:

> ‘An acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication’ (1).

Exacerbations are expressed as short periods of increasing symptoms often caused by bacterial and/or viral respiratory infection or environmental pollutants (25,26). Furthermore, the exacerbations are an important cause of the health impairment, morbidity and mortality in COPD (26).

The autoimmunity hypothesis reflects the similarities of pathologic and clinical characteristics with other autoimmune diseases in some self-perpetuating process that fuels the inflammatory response (19). Animal studies present strong evidence that chronic cigarette smoke exposure is sufficient to initiate an autoimmune response (27).

The Dutch hypothesis is that asthma and COPD have some common genetic and environmental risk factors (28). This was described in network overlap in pathobiology by Kaneko in the search for common pathways underlying asthma

and COPD (29). A recent large Genome Wide Association Studies (GWAS) concluded that:

> 'Our findings either suggest that there is no common genetic component in asthma and COPD or, alternatively, different environmental factors, like lifestyle and occupation in different countries and continents may have obscured the genetic common contribution' (30).

The normal lung function is highly heritable involving several genes (31). Genes play a role in the COPD development as well. Although the best known genetic variant alpha-1-antitrypsin deficiency only account for few percent of COPD cases (32,33). Several studies have been performed to identify additional genetic variants accounting for COPD and several genetic variants have an impact on the COPD development (34), but in summary these genetic variants only account for few percent of the variance according COPD development. Nevertheless the genetic studies in COPD are important to reveal causal genetic variants to discover new molecular targets for prevention, diagnosis, and treatment (34).

Identification and reduction of risk factor exposures are key elements in prevention and treatment of COPD (1,14). As the accelerated rate of decline in the lung function levels off in smokers with smoking cessation (14).

1.3. OCCUPATIONAL COPD

COPD develops slowly and as the airflow obstruction is chronic with no reversion when exposure is discontinued, the occupational COPD is based on elevated prevalence and risk observed among exposed workers compared to non-exposed workers (35). Several studies and reviews have addressed the issue of occupational exposure and COPD development despite variable terminology, case definitions, and exposure assessment. Recently, a meta-analysis provided a pooled estimate from 11 studies for the association between VGDF and COPD, odds ratio (OR) 1.43 (95% confidence intervals (CI): 1.19;1.73) regardless of some methodological differences (36). However, only few population-based studies have addressed the issue of occupational exposure solely among women.

Some reviews have focused on selected exposures (37,38) while most have addressed a large variety of exposures from different occupational settings (35,39-48). In the eighties Becklake concluded that occupational exposure to dust and/or dust and fumes may have a causal link to the pathogenesis of COPD, often relying on studies in which work-related factors were included as confounders to be adjusted for in analyses of smoking effects (39,40). Among coal miners Coggon and Newman Taylor concluded that there was a significant association between exposure to coal dust and the development of chronic airflow obstruction (38). The

reviews highly emphasis occupational exposure as a causal factor for COPD (35,41-45,47).

The question of causality is often based on Sir Bradford Hill's criteria from 1965 of strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (49). When the issue of causality is established or accepted the extent of occupational exposure to COPD can be recognised as the population attributable fraction (PAF). In this context PAF is the fraction of COPD cases that are preventable if all occupational exposures were eliminated (50). A review from the ATS quantified the work-related risk to the general population and concluded that approximately 15% of COPD could be attributable to occupational exposure (35), and the evidence is growing (44,45).

As smoking is an essential risk factor for COPD, the association of occupational exposure to COPD is especially interesting among never smokers. An ATS official statement on COPD among non-smokers from 2010 concluded there was sufficient evidence to infer a causal relationship between occupational exposures and development of COPD (10).

Nevertheless, the PAF is pointless if the actual exposure not is amenable to intervention. In a public health perspective the occupational exposure is potential to intervene at different levels by e.g. invention, education and rationale of personal protection and reduced primary exposure in general regulation of work conditions and procedures in prevention and modifying disability risk.

2. AIMS

The thesis aim to address the association between occupational exposure and COPD in a population-based cohort of Danes aged 45-84-years.

The specific aims for the included original research articles or manuscripts in this thesis are specified for each included articles; Paper I-IV:

Paper I The aim was to estimate the prevalence of COPD and analyse the association between COPD and prior occupational exposure to vapour, gases, dust and fumes (VGDF).

Paper II The aim was to estimate the prevalence of COPD, and analyse the association and population attributable fraction of occupational COPD among women.

Paper III The aim was to analyse for the association between occupational exposure and COPD among never smokers and estimate the corresponding population attributable fraction of the occupational exposure.

Paper IV The aim was to analyse for changes in lung function over time and estimate the incidence of COPD and associations to VGDF in a longitudinal study.

3. MATERIAL AND METHODS

3.1. DESIGN AND SETTING

The study is based on data from the North Jutland COPD Prevention Study (NCPS) (51). NCPS is a population-based cohort with baseline data collected in the period October 2004 - September 2006. The geographical setting at baseline was outlined as two former counties in Denmark; North Jutland and Viborg. Aalborg is the largest city in the area with approximately 120,000 inhabitants in 2004 (Figure 3.1). In January 2005 these two counties together counted approximately 299,000 inhabitants in the study age band of 45-84 year old participants, representing 14% of Danes in this age group.

In Denmark all citizens have free access to medical care provided by a general practitioner (GP). All 480 GPs in the two counties were invited to contribute in the recruitment of participants to the NCPS. In the end 155 GPs (32%) were interested and willing to invest their time and involvement in the study. The 155 GPs were situated in 89 practices (GPP) with a mixed urban and rural distribution (Figure 3.1).

Figure 3.1: Geographical setting of the study. Left; Denmark with the two counties highlighted. At the top is North Jutland county and below Viborg county. Right; Each participating general practitioner practice (89) marked in an enlarged copy of the two counties (84 marks and 5 parallel addresses).

3.2. POPULATION

3.2.1. BASELINE

The Danish individual personal 10-digit Civil Registration System (CPR) was used to select a random sample of persons aged 45–84 from each GP. The sample was age and sex stratified with an overweight of elderly and men, based on the expected Danish prevalence of COPD in 10-year groups (52). From each GP 86 subjects were randomly selected in the Civil Registration System. Nevertheless, some GPs were unable to accomplish the amount of subjects in the selected age and sex distributions entailing missing invitations (n=243).

The 13087 selected subjects received an invitation by mail in which they were requested to contact their general practitioner in order to participate in the study. With a response rate at 36%, 4742 participants entered the study. Participants with a prior lung cancer were excluded (n=25), leaving 4717 participants for analyses at baseline. The flow chart illustrates the entire enrolment of the baseline study population and throughout the follow-up study (Figure 3.2).

3.2.2. FOLLOW-UP

Follow-up data were collected between October 2008 and August 2010 in the same way as baseline data. Four GPP were not motivated to participate in the follow-up study, which excluded their 206 eligible baseline participants. These participants were assigned as non-responders, although they didn't receive an invitation at follow-up. Additionally 207 baseline participants passed away before the time of follow-up. The remaining participants included at baseline were sent a mail invitation and requested to contact their general practitioner again to participate in the follow-up study. The response rate at follow-up was 58%. The follow-up data consisted finally of 2624 participants, including 33% females. In the final follow-up population seven were excluded due to missing lung function test at baseline and 120 excluded due to COPD at baseline. COPD at baseline was defined by spirometry according to the method of Lower Limit of Normal (LLN), further described in paragraph 3.5, page 31.

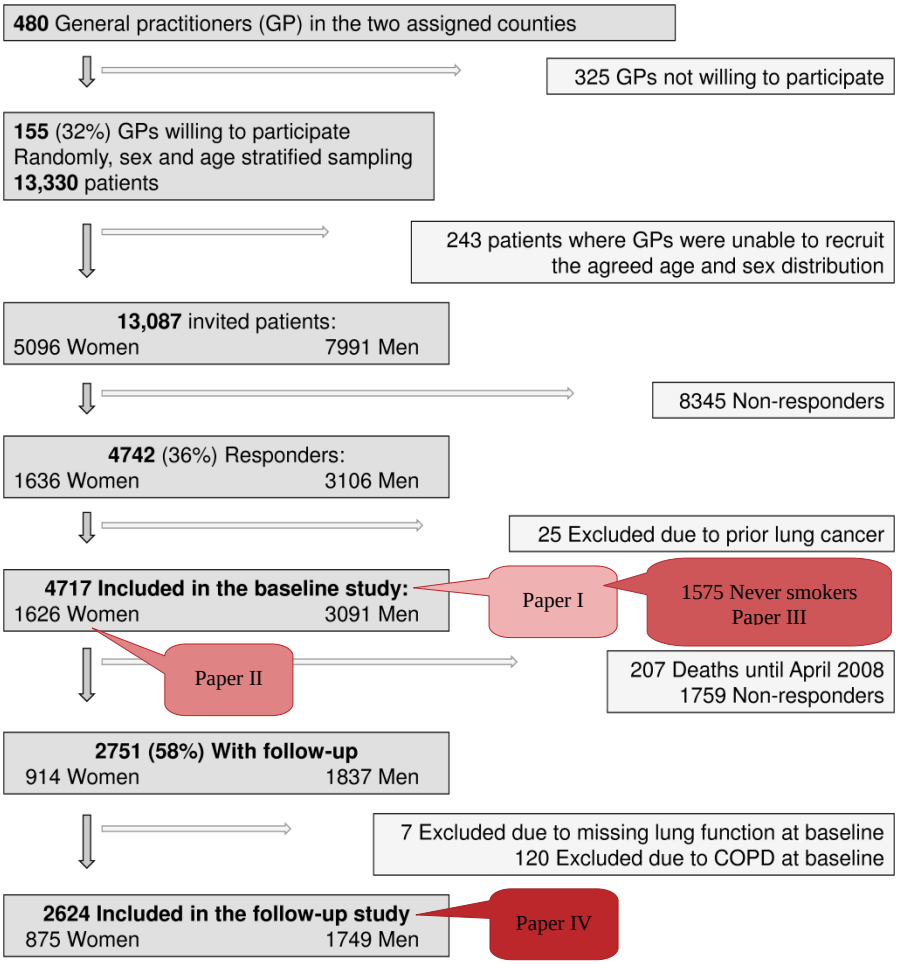

Figure 3.2: Flow chart of the study population throughout follow-up, 2004-2010, and indication of the populations included in each of the Papers in the thesis.

3.3. DATA

Baseline data consisted of a self-administered questionnaire, medical examination and a blood sample. The questionnaire included items of education, work, family history of lung disease, medical information, smoking and alcohol habits, asthma and allergy. The medical examination included blood pressure, height, weight, waist and hip measurements, and spirometry tests to assess the lung function by forced expiratory volume per second (FEV_1) and forced vital capacity (FVC). Asthma was assessed by the question: "Have you ever had asthma?" The form for medical examination and the questionnaire are included as Appendix A, page 65 (in Danish). The established biobank were collected for later analysis. Thus venous blood samples were collected in EDTA glasses (anticoagulant) and stored as whole blood at -20°C and stored at the Laboratory of Stem Cell Research, Aalborg University, Denmark.

Longitudinal data was collected approximately four years after the baseline data and consisted of a less comprehensive questionnaire and a similar medical examination without a new blood sample. The form for medical examination and the questionnaire are included as Appendix B, page 71 (in Danish).

3.4. SPIROMETRY AND REFERENCE VALUES

Pulmonary function tests were accomplished at the GP visits at baseline and follow-up by spirometry. The spirometry was performed by the GP or a trained member of the practice staff with the general practitioners own spirometer. Volume and time calibration of the spirometers was performed before study start and every six months by trained staff using a one litre syringe. Adequate spirometry test instructions followed the statement from the ERS (53) and the standard from ATS (54). For participants with a FEV_1/FVC ratio below 0.70 a reversibility test was performed with eight inhalations of Combivent (1 dose=100 µg salbutamol and 20 µg ipratropium) and assessed after 30 minutes.

The Global Lung Function 2012 Equations (55) in the "GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3" (56) was used as reference population. This equation takes age, sex and ethnicity into account to estimate the subsequent applied z-scores.

Based on the longitudinal data we assessed the annual decline in lung function and incident cases of COPD. In that cohort we excluded baseline COPD cases. The individual annual change in lung function was expressed by FEV_1 and FVC and calculated as follow-up data minus baseline data divided by the individual follow-up time.

3.5. COPD DEFINITION

We defined COPD by lung function measurements; FEV_1 and FVC. To assess the COPD diagnose the method of LLN was used. This approach for the FEV_1/FVC ratio is recommended concurrently by the ERS and ATS (57). In a screening setting of normal subjects the LLN is the 2.5^{th} centile (z-score = -1.96) (55). To distinguish subjects with at least moderate airway obstruction we added the screening criterion of the LLN for FEV_1 of a z-score = -2.0 (rounded 2.5^{th} centile) as recommended by Quanjer et al. (58). COPD defined by LLN was estimated using the pre-bronchodilator values.

Data was additionally presented based on the GOLD criteria with a fixed FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value (moderate airways obstruction; GOLD 2+) (3). This additional definition was included for possible comparison with prior studies and for discussion of methods. COPD defined by GOLD was estimated using the post-bronchodilator values if the pre-bronchodilator FEV_1/FVC ratio was <0.70 otherwise pre-bronchodilator values were used.

3.6. SMOKING

Smoking habits were assessed from the baseline and follow-up questionnaires. Different smoking variables were estimated; smoking status, duration of smoking and a cumulated smoking exposure. Smoking status was reported in a dichotomous variable as never-ever smoking or at three levels never-ever-current smoking. The smoking duration was assessed as years of smoking, and the cumulated smoking exposure as smoked pack-years. Pack-years were defined as the number of cigarettes smoked per day multiplied by the number of years smoked divided by 20. Pack-years were reduced to three levels of smoked pack-years: below 10, 10-20, and above 20 pack-years, respectively. In conversion of different types of smoking to the equivalent amount of cigarettes the clinical used equation from Aalborg University Hospital was used, as stated by the following equations: one cheroot=three cigarettes; one cigar=four cigarettes, one pipe bowl=three cigarettes, and a package of pipe tobacco (50 gram)=17 pipe bowls.

3.7. OCCUPATIONAL EXPOSURE ASSESSMENT

The occupational exposure assessment was based on a self-administered questionnaire validated by additionally restriction to a priori specialist identified jobs with an occupational exposure.

3.7.1. SPECIALIST

Two specialists in occupational medicine addressed an occupational exposure to the Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) (59). A priori all 372 DISCO-88 codes were evaluated and codes with known presence of occupational exposure to dust, gas, vapours and or fumes were identified. Final decision of identified codes was agreed upon by the two specialists. The final list of the 72 identified DISCO-88 codes is included as Appendix C, page 75 (in Danish). The self-reported jobs with an occupational exposure were then restricted to the selected DISCO-88 codes. The 72 DISCO-88 codes were distributed as 34 within organic dust, 20 within inorganic dust, 3 within fume/gas, 5 within vapour, and additional combination of exposures; 2 within organic and inorganic dust, 7 within inorganic dust and fume/gas, and 1 within inorganic dust, fume/gas and vapour. The complete list with English job descriptions is included in Paper I, Supplementary Table S1 (Appendix E, page 104).

3.7.2. QUESTIONNAIRE

The participants were asked for job titles and duration of their longest held jobs with an exposure to organic dust, inorganic dust, fume/gas, and or vapour, respectively. Furthermore, for each exposure category the participants could state up to three longest held job titles and appertaining durations. Thus, each participant could in theory state three jobs in each of the four exposure categories equal to 12 held jobs with an occupational exposure. Each job was reported with duration in five-year spans: ≤5 years, 5-9 years, 10-14 years, 15-19 years, and ≥20 years. The total duration of employment per exposure category was then calculated to define four levels of cumulated duration of exposure: no exposure (0 years), low exposure (<5 years), medium exposure (5-14 years), and high exposure (≥15 years). For each of the exposure categories, the total period of employment was calculated by adding the mean years of each stated employment as illustrated with different job combinations in each row in Figure 3.3.

Exposure	1	2	3	Time	Mean
NO	O	O	O	0	0
LOW	L	O	O	>0-<5	<2.5
	L	L	O	>0-<10	<5
MEDIUM	L	L	L	>0-<15	<7.5
	M	O	O	5-14	9.5
	M	L	O	>5-18	<12
	M	L	L	>5-22	<14.5
HIGH	M	M	O	10-28	19
	M	M	L	>10-32	<21.5
	M	M	M	15-42	28.5
	Any high combination			min. 15	min. 15

Figure 3.3: Achievable job combinations within each exposure category. NO/O: no occupational exposure; LOW/L: low occupational exposure; MEDIUM/M: medium occupational exposure; HIGH: high occupational exposure. Time: years. Mean: mean years worked with a particular occupational exposure, marked means indicate the defined exposure levels.

In the combined VGDF exposure the level of occupational exposure was estimated in a slightly different way. When summarising the four exposure categories in one overall combined VGDF occupational exposure according to the possible exposure from each specific exposure category, the "low exposure" was defined to have specific low exposures only, "medium exposure" to have specific medium exposure, but no high exposures, and finally "high exposure" to have any specific high exposure. This is illustrated in Figure 3.4.

	1	2	3	4
No	0	0	0	0
Low	Any low combination without medium or high exposure			
Medium	Any medium combination without high exposure			
High	Any high combination			

Figure 3.4: Structure of the combined vapour, gas, dust and fume (VGDF) exposure. 1-4 reflect the four exposure categories of organic dust, inorganic dust, fume/gas, and vapour, respectively. No/0 illustrates no occupational exposure. Small letters low, medium, and high express the level of occupational exposure in each exposure category. Capital letters Low, Medium and High express the level of the combined VGDF occupational exposure.

3.8. DATA MANAGEMENT

In data management the a priori identified DISCO-88 codes were assigned to jobs included in the DISCO-88 description from Statistics Denmark (59). For each participant all applicable DISCO-88 codes within the four exposure categories were assessed at the same time to provide the best job indication. We experienced several participants who assigned jobs in mistaken exposure categories e.g. all exposed jobs reported at the first occasion in the questionnaire (e.g. welders exposed to organic dust). Additionally, in no accordance with the specialist identified DISCO-88 codes many more jobs were assigned as occupational exposed. Thus the specialist identified DISCO-88 codes persistently exceeded the self-reported occupational exposure in the exposure assessment. The final list of included job titles within each DISCO-88 code is included as Appendix D (in Danish); D.1: Organic dust, page 79, D.2: Inorganic dust, page 84, D.3: Fume/gas, page 88, and D.4: Vapour, page 91.

No general imputation of missing data was conducted, but few essential missing data were imputed in the data set. Height was missing or evidently wrong in four participants, one was imputed from follow-up data and the others estimated as a mean height of similar participants according to sex, age and weight. In some questionnaires there was discordance between the stated smoking status and the present number of smoked cigarettes; in these cases the number of smoked cigarettes exceeded the stated smoking status.

3.9. STATISTICS

Statistical analyses were conducted in Stata 12.1 (StataCorp LP, 2011). The significance level was set at 5%. The 95% CI was calculated using a normal approximation. The chi-square test and Fishers exact test for categorical variables was used to assess differences between sub-groups of the study population. While non-parametric analysis of Kruskal-Wallis was used for non-normally distributed data. The McNemar test was used for matched data to compare the two methods of assessing COPD; the LLN and GOLD methods as defined earlier. Baseline COPD prevalence was age-standardised to the Danish population, January 2006. At baseline (Paper I-III) associations of occupational exposure to COPD were analysed univariate and in mixed random effect logistic regression models (60) with GPP as random variable. Likelihood ratio tests were performed for possible interaction of variables in the models. The PAF was estimated on the basis of the adjusted OR by the following equation; proportion of cases exposed*(OR-1)/OR (50). In the equation OR was used as a proxy for the relative risk.

3.9.1. PAPER I

The mixed regression model was adjusted for pack-year, sex and age as fixed effects. Sensitivity analyses were performed by recoding all the missing occupational exposures (i) into no exposure and (ii) into high exposure, or by (iii) excluding all participants with prior self-reported asthma.

3.9.2. PAPER II

The mixed regression model was adjusted for pack-year and age as fixed effects. Sensitivity analyses were performed by (i) excluding all participants with self-reported asthma and (ii) include mild COPD in the LLN COPD definition (FEV_1/FVC 2.5^{th} centile, but lacking the FEV_1 LLN criteria) and (iii) exclude women with a tentative occupational exposure.

3.9.3. PAPER III

Among the never smokers in Paper III the mixed regression model was adjusted for sex and age as fixed effects. Sensitivity analyses were performed by excluding all participants with self-reported asthma, and additional adjustment for passive smoking.

3.9.4. PAPER IV

The annual change (Δ) in FEV_1 and FVC was reported as mean and standard deviations (SD), and analyses of variance were used to compare groups of normally distributed means. The annual change in FEV_1 and FVC were stratified by age ($<$ and $\geq$ 60 year at follow-up). The choice of 60 years was applied to take the possibility of voluntary early retirement pension in these birth cohorts into consideration. Thus the youngest group was considered as a proxy for an ongoing working population throughout the follow-up period if they reported no occupational change in-between baseline and follow-up. The COPD incidence was age-standardised to the Danish population, January 2010. When estimates were based on the GOLD defined COPD, additional 120 participants with baseline GOLD defined COPD were excluded. Mixed Poisson regression model with GPP as random variable was used to estimate the association between incident COPD and occupational exposures with adjustment for pack-years, sex and age, reported as incidence rate ratio (IRR). Due to few COPD cases in the youngest age groups, age was included as a continuous variable. Additionally, the IRR was adjusted for asthma status in-between baseline and follow-up. Analyses of the combined VGDF occupational exposures were additionally restricted to organic dust, as organic dust

was the main single occupational exposure group. Data didn't reveal the power to analyse the other sub-groups of occupational exposure.

3.10. ETHICS

The NCPS-study has been performed in accordance to the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

4. SUMMARY OF RESULTS

The main results from each Paper are summarised below while more detailed results are available in the appended Papers (Appendices E-H), nevertheless the occupational exposure is described more detailed than in the Papers. This section will focus on COPD defined by LLN, while association to the GOLD defined COPD, additionally, is described in the appended Papers. We observed no statistical significant interaction terms among the used variables in the different models. Furthermore, few additional PAF results are presented at this point, as these were not included in Paper I; although they are important for the external validity and evaluation of the study.

The PAF caused by occupational exposure in COPD was initially addressed among women and never smokers (Paper II and III), but not in the whole study population (Paper I). The PAF of an occupational exposure to VGDF calculated among the whole study population in contribution to COPD was estimated to 15% (95% CI: 3;28) and similar when limiting the exposure to the main single exposure of organic dust, 15% (95% CI: 3;27).

4.1. OCCUPATIONAL EXPOSURE

The occupational exposure assessment was equal in all four papers. As described in Paper I 372 DISCO-88 codes excist and 72 of them were a priori selected as exposed to any VGDF. In this study population only 54 (75%) DISCO-88 codes were identified. The included codes were distributed as 27 of the 34 identified DISCO-88 codes with relevant exposure to organic dust, likewise 12 of 20 to inorganic dust, 2 of 3 to fume/gas, 5 of 5 to vapour, 0 of 2 to combined organic and inorganic dust, 7 of 7 to combined inorganic dust and fume/gas, and 1 of 1 to combined inorganic dust, fume/gas and vapour (Appendix E: Supplementary Table S1, page 104).

About half of the population, 49%, reported no DISCO-88 code with relevant exposure, 31% reported one DISCO-88 code with relevant exposure, and 15% (n=693) reported between two and six DISCO-88 codes with relevant exposures, while 5% did not answer the occupational question. However, there were significant gender differences in the assessed occupational exposure, $p<0.001$ (Table 4.1). The majority of women (75%) had no relevant occupational exposure to VGDF, while men more often experienced exposures from more than one exposure category (Table 4.2) and 39% had a relevant high exposure to VGDF (Table 4.3). Organic dust was the most frequent occupational exposure in both men (56%) and women (19%), and out of all participants with a combined VGDF exposure, 80% had an organic dust exposure among the men and 90% among the

women. The distribution of the occupational exposures is separately illustrated by sex and level in Paper I (Appendix E: Figure 2, page 98). As addressed in Table 4.2 the figure underlines the fact that many participants (15%), especially men, have several exposures since the exposure pillars in the figure section with VGDF are less than the sum of the specific exposure pillars within each category.

Table 4.1: Number of assigned DISCO-88 codes by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Number of assigned DISCO-88 codes				
0	1226	(75)	1104	(36)
1	248	(15)	1203	(39)
2	29	(2)	445	(14)
3	2	(0.1)	150	(5)
4	0	-	52	(2)
5	0	-	13	(0.4)
6	0	-	2	(0.1)
No answer	121	(7)	122	(4)
Total	1626		3091	

DISCO-88: The Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) (59).

Table 4.2: Number of assigned VGDF categories by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Number of assigned VGDF categories				
0	1226	(75)	1104	(36)
1	265	(16)	1338	(43)
2	14	(1)	373	(12)
3	0	-	132	(4)
4	0	-	22	(1)
No answer	121	(7)	122	(4)
Total	1626	(100)	3091	(100)

VGDF: Vapour, gas, dust and or fume.

Table 4.3: Distribution of the combined VGDF assessed exposure by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Dose of VGDF defined by time				
No exposure	1226	(75)	1104	(36)
Only low exposure	61	(4)	309	(10)
Medium, exposure (and no high)	63	(4)	360	(12)
Any high exposure	155	(10)	1196	(39)
No answer	121	(7)	122	(4)
Total	1626	(100)	3091	(100)

VGDF: Vapour, gas, dust and or fume. Low: Exposure, but <5 years. Medium: 5-14 years of exposure. High: ≥15 years of exposure.

4.2. PAPER I

Paper I included the whole baseline study population (N=4717). The lung function test was missing in 20 participants leaving 4697 with a pre-bronchodilator spirometry. The age-standardised LLN defined prevalence of COPD was 5.0% (95% CI: 5.0;5.0) and significant lower among women compared to men, 4.6% (95% CI: 4.6;4.6) and 5.0% (95% CI: 5.0;5.0), respectively (Appendix E: Table 2, page 99), equal to 279 participants with COPD.

In a matched comparison of the two methods for defining COPD (LLN and GOLD) there was a significant difference with 173 discordant diagnoses between the LLN (17 only COPD by LLN) and GOLD (156 only COPD by GOLD) definitions (Appendix E: Table 3, page 100).

The associations between occupational exposure to VGDF or the organic dust variable and COPD, revealed from the mixed regression model, were increased for the occupational exposures. As well as for the additional known risk factors for COPD as smoking, age and gender (Appendix E: Table 4, page 100). The adjusted odds ratio (ORadj) for medium VGDF exposure was 1.61 (95% CI: 1.03;2.51), while the ORajd for high organic dust exposure was 1.56 (95% CI: 1.09;2.24). Significant trends in exposure level were also present in these associations, p=0.031 and p=0.017, respectively. As agriculture was the main exposure in the organic dust category with 1495 out of 1926 occupational reports (78%) the analyses were restricted to this exposure as well, and ORadj and trend remained significant; 1.59 (95% CI: 1.08;2.33), p<0.02, respectively. No associations to COPD were seen in the other occupational exposures of inorganic dust, fume/gas and vapour in the study

4.3. PAPER II

Paper II included the women (N=1626) from the baseline study population. Among the women 35% of the identified 72 DISCO-88 codes were applied (25 DISCO-88 codes) and the distribution is described in Table 4.4 with the majority of codes and participants in agriculture. In all, 279 women were assigned with a relevant occupational exposure by the specialist assessed exposure. Lung function measurements were present in 1617 with a pre-bronchodilator spirometry and 76 had COPD defined by LLN.

In the paired comparison between the two criteria for defining COPD there was a significant difference in the oldest age group (75-84 years) where more subjects had COPD using the GOLD definition (15.3%) compared to the LLN definition (7.5%), p<0.001.

Table 4.4: Distribution of the a priori selected DISCO-88 codes with known relevant occupational exposure to organic dust, inorganic dust, fume/gas, and vapour, among the 1626 participating women [*], and job descriptions of the most frequently applied codes (≥*10* participants).

Job description [†]	DISCO-88	Assigned exposure				
		Organic dust	Inorganic dust	Inorganic dust and Fume/gas	Fume/gas	Vapour
Field crop and vegetable growers	6111	*12*				
Dairy and livestock producers	6121	*17*				
Market-oriented crop and animal producers	6130	*138*				
Welders and flamecutters	7212				*20*	
Wood-products machine operators	8240	*10*				
Fibre-preparing-, spinning- and winding-machine operators	8261	*17*				
Farm-hands and labourers	9211	*53*				
Number of applied DISCO-88 codes among the women (sum 25)	25	14	4	3	1	3
Number of applied DISCO-88 codes among the women with ≥*10* participants	7	6			1	

DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988 (59).

[*]Missing occupational information, n=*121*. [†]Statistics Denmark (3 April, 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx. *Italic; Number of participants.*

The occupational exposures were dichotomised as never or ever occupational exposed women to achieve a better power in the study, due to few exposed women. The results from the mixed model regression analyses on the association between occupational VGDF, organic dust exposure, and COPD are presented in Paper II (Appendix F: Table 2, page 118). The ORadj in VGDF and organic dust exposure

revealed a significant increased association to COPD, 1.98 (95% CI: 1.06;3.69) and 2.05 (95% CI: 1.04;4.08), respectively. The study PAF for COPD was estimated to be 14% in the VGDF exposure and 15% when restricted to the organic dust exposure. Whereas too few women had an occupational exposure to inorganic dust (n=9), fume/gas (n=23), and vapour (n=17) for analyses as illustrated in Paper II (Appendix F: Figure 2, page 116).

In sensitivity analyses the occupational specialists identified 24 women with a tentative farming exposure as 'assisting wife', when excluding this group in the analyses of organic dust the association was maintained; ORadj 2.15 (95% CI: 1.06;4.37). Excluding women with prior asthma (n=174) increased both associations to occupational VGDF and organic dust exposure to COPD, ORadj 2.81 (95% CI: 1.36;5.79) and 2.99 (95% CI: 1.37;6.55), respectively.

4.4. PAPER III

Paper III included the never smokers from the baseline study population (N=1575). Occupational exposure were present in 658 (42%) of the never smokers in between 1 (72%) and 5 jobs. COPD defined by LLN was present in 26 participants equal to a prevalence of 1.7%.

Table 2 in Paper III (Appendix G, page 133) show the adjusted associations between the occupational exposures and COPD. Participants exposed to VGDF and organic dust had an increased risk of COPD, ORadj 3.69 (95% CI: 1.36;10.04) and 2.94 (95% CI: 1.05;8.22), respectively. An important confounder among never smokers is passive smoking, but only few (n=45) had never experienced this. Passive smoking was not associated to COPD and only to a minor extent additional adjustment changed the estimates. Excluding 145 never smokers with prior self-reported asthma (reported as never or ever) in the analyses provided similar associations; VGDF: ORadj 2.64 (95% CI: 0.70;9.92), organic dust: ORadj 3.43 (95% CI: 0.86;13.70).

The study PAF for COPD among never smokers caused by occupational exposure was 48% (95% CI: 30;65) for VGDF exposure and 41% (95% CI: 19;62) for organic dust exposure.

4.5. PAPER IV

Paper IV was the four-year longitudinal study with follow-up data from 2008/2010 focusing on COPD incidence and annual decline in lung function. The mean period of follow-up time was 3.7 years (SD 0.35; range 2.4-5.0 years) and equal across genders. Follow-up participants and non-participants were compared in the Paper (Appendix H: Table 1, page 146) and equal according occupational exposure,

although participants were younger, had better lung function and smoked less. COPD cases at baseline were excluded (n=120) thus 2624 were eligible, but additional 28 lacked spirometry at follow-up and finally 2596 participants with spirometry were included.

Decline in lung function was addressed in the Paper (Appendix H: Online Supplementary Table S1, page 155). Briefly the overall annual mean (±SD) change in lung function in men was ΔFEV_1 -50 mL/yr (±94) and ΔFVC -58 mL/yr (±133) and in women -31 mL/yr (±69) and -38 mL/yr (±105). No analyses reached statistical significance. In men (<60 years) with combined exposure from occupation and smoking there was a borderline trend in association in FVC (VGDF; p=0.11, organic dust; p=0.06) and a 2-fold decrease in FVC, and partly in FEV_1 when comparing non-smokers having no occupational exposure with smokers having an occupational exposure.

New-onset COPD was identified by spirometry in 1.5% (95% CI: 1.0;1.9) of subjects (n=38) (men 1.7% (95% CI: 1.1;2.4), women 0.9% (95% CI: 0.3;1.6)). The age-standardised estimates were 0.9% (95% CI: 0.9;0.9) (men 1.0% (95% CI: 1.0;1.0), women 0.7% (95% CI: 0.7;0.7)). In comparison of the two definitions of COPD there was a significant difference, p<0.01.

The IRRs from the regression analyses are summarised in the Paper (Appendix H: Table 3, page 149). In the adjusted IRR occupational exposures were associated with COPD; low VGDF exposure 3.71 (95% CI: 1.17;11.8), high VGDF exposure 2.62 (95% CI: 1.06;6.48), low organic dust exposure 3.24 (95% CI: 1.07;9.83), but with no clear exposure-response relation. As expected other known risk factors of COPD as smoking and age were associated to COPD as well. Sub-analyses were performed with adjustment for asthma status between baseline and follow-up. This increased the low VGDF association to IRR 4.57 (95% CI: 1.38;15.15) while the high exposure slightly decreased to IRR 2.43 (95% CI: 0.92;6.38), p= 0.07. A similar pattern was revealed for organic dust (low exposure IRR 3.77 (95% CI: 1.21;11.79).

5. DISCUSSION

In this population based study including both cross-sectional and longitudinal analyses the VGDF exposure consisted predominantly of organic dust. COPD was associated to occupational exposure also in subsets of never smokers and women, but without a clear exposure-response relation in the longitudinal analysis.

5.1. PAPER I

We found an age-standardised prevalence of COPD of 5.0%. This is in accordance to other studies from Europe and US where the prevalence is reported to be between 4.5 and 10% using different diagnostic criteria (61-65).

In the present study occupational VGDF and organic dust exposures were in a dose dependent manner associated to the prevalence of COPD. The associations were similar when restricting the analysis from organic dust exposure to agriculture exposure alone. The positive associations within the organic occupational exposure may reflect the dominating position of agriculture in Northern Denmark as the major occupation for exposure to VGDF in the study. Several cross-sectional studies have found an association between occupational organic dust exposure in agriculture and COPD (66-68). We found a weaker association between high organic dust exposure and COPD when excluding subjects with prior self-reported history of asthma ORadj 1.47 (95% CI: 0.92;2.34), trend p=0.15. In the SAPALDIA study, including only non-asthmatics, the incidence rate ratio was 2.76 (95% CI: 1.32;5.75) for COPD with any organic dust exposure in ever smokers (69). The differences in observation might be due to difference in the concentration of the exposure, low statistical power in our study or may reflect healthy-worker selection where subjects with possible prior asthma leave farming to more manageable jobs with lower occupational exposures.

The calculated PAFs of 15% in subjects exposed to both VGDF and organic dust were in accordance with prior estimates of the burden of occupational exposure (PAF not included in Paper I) (35,44,45).

5.2. PAPER II

The age-standardised prevalence of COPD among women was 4.6%, and in accordance with other studies from Europe and US where the prevalence in women is reported to be between 4 and 7% using different diagnostic criteria (62,64,65). Our findings is also in accordance with the data from the review by Halbert et al. that estimated a pooled female prevalence from 27 studies to be 5.6% (95% CI: 4.4;7.0) (70) and even more so when defining COPD as the clinical used $FEV_1/FVC<LLN\ 5^{th}$ centile (z-score < -1.64) and $FEV_1<LLN$ -2. Then the age-standardised prevalence was 6% (n=93).

The association between occupational exposure and COPD solely in women is studied by few when defining COPD on lung function measurements. Matheson et al. estimated a strong association between COPD and organic dust exposure among women, OR 7.43 (95% CI: 2.07;26.7), but this estimate was based on a broader definition of COPD (71). Studies by Beck et al. and Elwood et al. estimated a significant decline or lower FEV_1 among female cotton textile workers (72,73). We found stronger associations to COPD when excluding subjects with prior self-reported history of asthma. Our estimates are in accordance with the SAPALDIA study where only non-asthmatics of both genders were included. They found an incidence rate ratio of 2.76 (95% CI: 1.32;5.75) for any organic dust exposure in ever smokers and COPD (69). Although females have been shown to perform work with less respiratory hazards compared to males within the same occupation and industry (74) few studies have analysed for PAF for COPD associated to occupational exposure in females, and none in the same age group as in the present study. Blanc and Torén estimated in their review from 2007 PAF for COPD to be 0 and 1% (44), but these were based on a younger population exposed to dust, and gases and fumes (75). Our estimates (14% for COPD in exposed to VGDF and 15% in exposed to organic dust) are in correspondence with the 15% PAF for COPD calculated in former studies (76), but predominately based on men.

5.3. PAPER III

COPD was increased more than three times in never smokers when occupationally exposed to VGDF and three fold for organic dust despite the low prevalence of COPD (1.7%). However, the calculated associations between occupational exposure and COPD have wide CI due to few cases in each stratum. Our prevalence estimate was low compared with the prevalence in never smokers from the BOLD study (0-11%) (13). Here COPD was defined by GOLD criteria stage II or higher in a slightly younger population. When converting our prevalence estimate based on LLN criteria to GOLD criteria the prevalence of COPD increased to 3.4% reducing the difference in the prevalence between the studies. We have found the highest PAF among studies published in never smokers 48% (95% CI: 30;65) (63,76) and

higher than the PAF 43% (95% CI: 0;68) from the study by Weinmann (77) a smaller case-control study with similar definitions of COPD by LLN and an expert assessed occupational exposure as in the present study.

However, a big Chinese population-based study including 6648 never smokers found no significant association between self-reported occupational exposure and COPD defined by LLN, OR 1.29 (95% CI: 0.92;1.81) (78). This might be a result of non-differential misclassification moving the risk estimate towards null by incorrectly label low or no exposure jobs in the high exposure group and vice a versa.

5.4. PAPER IV

The age-standardised four-year incidence of COPD was 0.9%. This is in accordance with results from the US ARIC study where the three-year incidence was 2%, though obstruction was defined by LLN 5^{th} centile (79). We have applied the FEV_1/FVC LLN of 2.5^{th} centile instead of the clinical used 5^{th} centile to reflect a screening setting in our population-based study having no a priori indication of COPD.

The annual decline in FEV_1 and FVC revealed no statistical significance in any of the analysis. The short follow-up time and the observed wide range in variation might partly explain our findings. However, in men below 60 years of age the combination of occupational exposure and smoking caused a decline in FVC, with borderline statistical significant trends; VGDF p=0.11 and organic dust p=0.06. The study annual decline in lung function was lower, but with wider variation as compared with the ARIC study although our population was older (79). This might reflect differences in spirometry testing and equipment. However, ethnicity could also play a role. In the ARIC study 23% of the participants were black (79), compared to only Caucasians in our study.

Despite the short follow-up time prior occupational exposures were associated to incident COPD by 2-3 folds, but with no clear exposure-response relation. The ARIC study found no association with current or most recent occupation at baseline (79). In contrast, the SAPALDIA study found dose-dependent associations between VGDF in both LLN and GOLD defined COPD, and only highly exposed LLN were non-significant. The associations ranged from 1.1 to 4.0 (69) similar to the LNN association in the current study. Their occupational exposures were based on current job, duration of current job and a job exposure matrix. We used a cumulative job exposure from all held jobs and extracted the level of exposure based on mean total exposed years in the different jobs. These different approaches might explain the differences in associations. Furthermore, the differences could reflect national variation in the welfare system. In Denmark it might be easier to be

retrained, change job conditions or job compared with Switzerland, thus the reason why we find the association more pronounced in the low occupational exposure group might be due to a healthy worker effect. The high effect in the low exposed group could also be a consequence of age differential work procedures. As for instance in farming the younger workers perform the most hard, dirty and dusty tasks, while the elderly will concentrate on less strenuous and cleaner job tasks.

The differences between LLN and GOLD might reflect that GOLD defines too many COPD cases alone according to their age, which might dilute the association to the working exposure. Additional adjustment for asthma status between baseline and follow-up increased the IRR among the low occupational exposures using the LLN approach. Thus the results after excluding asthmatics emphasise the assumed healthy worker effect as they have known symptoms and might have changed their work tasks or jobs to more manageable tasks or jobs with lower occupational exposures because of these symptoms.

5.5. METHODOLOGICAL ISSUES

5.5.1. COPD

In epidemiologic studies the definition of disease is often simplified and not identical to the corresponding clinical diagnose. We defined COPD by lung function measurements. There is no 'gold standard test' to assess COPD by spirometry. Nevertheless, the LLN approach is recommended concurrently by the ERS and ATS (57). As opposed to the GOLD fixed method which is somewhat biased by participants age, sex and height (80). This difference was also revealed in the present study with increased prevalence of COPD among the women in the oldest age group calculated by the GOLD method compared to the LLN method. The LLN definition ensures that the participants do have a degree of airflow obstruction outside accepted population norms. However, the 2.5^{th} centile as a diagnostic criterion is a conservative approach aiming to minimize the percentage of false positives at the expense of an increased number of false negatives, as the population-based study is comparable with a screening situation and not related to symptoms and diagnosing.

To assess the COPD severity the ATS/ERS recommendation utilise the fixed FEV_1 percent predicted (57). In the present study we have analysed the data based on the recommendation by Quanjer et al. They recently published a new grading of the obstructive lung disease that is clinically relevant and free of biases related to age, height, sex and ethnic group (58). Adding the restriction of FEV_1 z-score <-2 we obtain a group of subjects having moderate airways obstruction, corresponding to the ATS/ERS moderate airways obstruction (58).

5.5.2. MEASURING COPD OR ASTHMA

In epidemiological studies the outcome of disease/diagnoses is often assessed through a 'gold standard test' to minimise inclusion of differential diagnoses as cases. No 'gold standard test' is available to differentiate between COPD and asthma by spirometry. According to the ATS/ERS standardisation of lung function testing from 2005 there is no evidence to clearly differentiate asthma and COPD patients by bronchodilator response (57). The response to bronchodilators varies within and between individuals (81) and when predicted reference values were established as pre-bronchodilator values; this included some overestimation of the reversibility of a low FEV_1/FVC ratio. In the present study the differential diagnoses of asthma was managed in sensitivity analyses by excluding participants with self-reported prior asthma, although asthma and COPD may occur at the same time. Asthma predisposes to the development of COPD (82,83) and asthma is also associated to the investigated exposures (84,85) and is a potential confounder. Excluding asthmatics as defined from the analyses might underestimate the true association to occupation as an inclusion of the subjects is likely to overestimate the association. The best estimate might therefore be in-between these ORs. In Paper I the ORadj including and excluding asthmatics were very similar while we saw a non-significant increase of the estimates in Paper II-IV. This difference in the sensitivity analyses between Paper I and Paper II-IV might be due to smaller populations in Paper II-IV resulting in less stabile risk estimates. Thus the findings does not contradict that the best epidemiological estimate of COPD risk is in between calculated figures including and excluding asthma.

5.5.3. OCCUPATIONAL EXPOSURE ASSESSMENT

The occupational exposures were assessed by a self-administered questionnaire on exposures and occupation validated with an expert judgement. This approach is considered more sound than questionnaires alone (86), and our results support that the often used self-reported exposures might be prone to bias. This or similar combined approaches are well established and have been utilized in several population-based retrospective studies (61,77,87).

Recall bias of occupational exposure might be introduced tending to overestimate the association between exposure and disease. Although the risk was considered low, as the questionnaires were filled out before the GP examination, and thus only participants with well known COPD might have been more aware of job exposures. As patients with mild COPD have vague or no symptoms this assumption was tested by estimating the association of mild COPD and high organic dust exposure which slightly increased the ORadj (1.88 (95% CI: 1.13;3.13). This result supports that our findings unlikely are skewed by recall bias. Furthermore, few Danes aged 45 to 84 have knowledge of an association between occupational exposure to

VGDF and COPD, and the a priori selected DISCO-88 codes and expert management of each job title into DISCO-88, without awareness of COPD status, have further blinded the exposure assessment. As the prevalence of COPD was the same (p=0.63) among participants that have answered questions on work exposure and among those that did not, selection bias according to the exposure seems not to be a problem in the study. Furthermore, COPD was the main outcome of the planned study (51) and not related to the occupational exposure so this issue would probably not have reduced the initial response rate into the study.

The approach with four exposure categories is a simplified exposure assessment without consideration of all exposure details according to specific agents and exposure quantity. Misclassification of exposure can thus not be ruled out, but if introduced it would be non-differential. The main occupational exposure of organic dust may reflect the dominating position of agriculture in Northern Denmark as a special Danish occupational exposure scenario.

5.5.4. SMOKING EXPOSURE

In the personal assessment of smoking we found no common conversion of different types of smoking to the amount of cigarettes. We have applied the equations clinically used at Aalborg University Hospital, Denmark. This was nearly the same equation as Bernaards et al. used in their comparison study of calculating pack-years prospectively and retrospectively (88).

Passive smoke exposure was only considered as a confounder in Paper III among the never smokers. Only few never smokers had never experienced an exposure to passive smoke either at home or at work (n=45), probably due to the current age group and former smoking habits and behaviour among smokers in the society. Passive smoking was assessed as never/ever exposed and was not associated to COPD and additional adjustment for passive smoking changed only the estimates to a minor extent. This is in contrast to the study of never smokers by Hagstad et al. who found an association between passive smoking and COPD (89). They defined COPD according to the GOLD method and adjusted for socioeconomic status, based on occupation, but not a possible occupational exposure which might confound their estimates.

5.5.5. STRENGTHS AND LIMITATIONS

The external study validity is considered to be high in a Western world setting with similar occupational distribution, due to expected similar occupational exposures. However, the major contribution of organic dust exposure might reflect a special Danish occupational exposure scenario.

The overall enrolled study population included more young women and fewer participants in the oldest group than among non-responders. This might introduce an age dependent healthier study population tending to underestimate the associations. On the other hand, the included study population was older than populations from other articles in this research field (69,71,79) although some results are unexpected as the non-significant results of the annual FEV_1 and FVC decline.

Spirometry error measurements have been managed by regular calibration, but the variations of brands among GPP were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements as recommended by the ERS and the ATS (57). Possible misclassifications of outcome would be of non-differential nature and tend to underestimate the associations. Some of the variability in between spirometer and operators was addressed by including the GPP as a random variable in the analyses. Moreover, when using a spirometrically-defined COPD some COPD patients with compliance difficulties might be excluded from the analyses possibly resulting in false low associations.

Information bias of exposure was probably reduced by using the specialist assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. A validation of the self-reported exposures uncovered a large discrepancy between the occupational specialists and the participants regarding relevant exposures due to the stated job titles. The job titles often were connected to the wrong exposure and, furthermore, the specialists assessed many of the job titles as having no occupational exposure. As a consequence a significant discordance in the four exposure groups was observed comparing the dichotomised expert assessed exposure and the self-reported exposure in the unrestricted data set (N=4717). Furthermore, this was emphasised in the sub-analysis in Paper II where 24 women with a specialist defined tentative exposure were excluded and slightly increased the association.

6. CONCLUSION

Occupational VGDF and organic dust exposure were associated to COPD including analysis in subsets of non-smokers and females although a clear exposure-response relation was not observed in the longitudinal analysis. More detailed in:

Paper I We found in this population-based study involving 4697 subjects an age-standardised prevalence of COPD of 5.0%. Organic dust exposure was in a dose-dependent manner associated to the prevalence of COPD, independent of smoking habits, although the study found no associations to other less-common exposures.

Paper II We found in this population-based study involving 1626 women an age-standardised prevalence of COPD of 4.6%. Organic dust exposure was associated to the prevalence of COPD, independent of smoking habits. The population attributable fraction of occupational organic dust and COPD among women was 15%.

Paper III We found that occupational exposure to VGDF and organic dust significantly increased the risk of COPD corresponding to a high PAF (VGDF 48%) indicating that occupational exposures contributes substantial to the burden of COPD in never smokers. The major contribution of organic dust exposure among the VGDF exposures in this study might reflect a special Danish occupational exposure scenario.

Paper IV We found that occupational VGDF and organic dust exposure to increase the incidence of COPD, but without a clear exposure-response relation. However, the study found no statistical significant impact of occupational exposure on the annual declines in FEV_1 and FVC.

7. PERSPECTIVES

The present study emphasise the major influence that exposures from occupation as VGDF and organic dust have on COPD, also among never smokers and women. These findings from the labour market in Denmark might indicate that even low exposures from work over time can have an impact on the development of COPD. The awareness by recognising these data ought to be transformed to preventive efforts to eliminate occupational COPD and thus improve public health.

Included in the study, but not as a part of the Thesis is analysis involving selected candidate genes. By introducing this kind of analysis in occupational settings inborn susceptibility and gene-environment interaction can be studied. As genetic variations previously have shown some impact on COPD in different cohorts the genetic variation might influence the associations between occupational exposures and COPD. The intensity of the occupational exposure is generally less and of lower intensity compared to smoking. The genetic variants might therefore have another or more pronounced/clear impact on COPD when combined with occupational exposures than with smoking exposure.

The focus is upon candidate genes selected from studies in the oxidative defence, GWAS and well-known genetic associations as in alpha-1-antitrypsin deficiency.

We have included:

- 17 genes/areas corresponding to 32 single nucleotide polymorphisms (SNP) analysed by TaqMan OpenArray genotyping system from Applied Biosystems.
- Gene deletion - copy-number variation (CNV) in two genes analysed by quantitative polymerase chain reaction (qPCR).
- Number of repeats in one gene analysed by fragment analysis.

Finally the genetic results is planned to be replicated in another Danish cohort, but in younger persons.

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9. APPENDICES

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APPENDIX A. BASELINE DATA ESTABLISHMENT - 2004 (DANISH)

Baseline data source from the GP examination and the participant self-administered questionnaire.

PATIENT NO.:

Lægeskema

Dato: _____

Patientinitialer: _____

CPR nummer: _____

BT: _____

Vægt: _____

Højde: _____

Taljeomkreds: _____

Hofteomkreds: _____

Blodprøve udtaget: Ja: Label påklæbes her

Nej: Angiv årsag: _____

Dette skema vedlagt resultat af spirometrien, patientskemaerne og underskrevet samtykkeerklæring (husk at patienten skal have en kopi) sendes til projektledelsen i den frankerede svarkuvert

Send blodprøven med label til Laboratoriet for Stamcelleforskning i den frankerede svarkuvert

Tak for hjælpen

Projektledelsen
21. september 2004

Kronisk obstruktiv lungesygdom i Nordjylland og Viborg Amter, Aalborg Sygehus, Århus Universitetshospital, Stengade 10,2 9000 Aalborg.

PATIENT NO.:

Medicinske oplysninger

Sæt venligst kryds ud for hvert spørgsmål:

Lider De af eller har De lidt af følgende sygdomme? (sæt kryds)

a. Blodprop i hjertet ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang _____

b. Hjertekrampe (angina pectoris) ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang _____

c. Anden form for hjertesvækkelse ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang _____

d. Forhøjet blodtryk ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang _____

e. Lungekræft ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang _____

f. Er De blevet opereret for lungekræft? ☐ Nej ☐ Ja

Hvis ja, hvor gammel var De? _____

g. Andre kræftsygdomme ☐ Nej ☐ Ja

Hvis "ja", hvilken _____

PATIENT NO.:

Familieoplysninger

1. Er der hos Deres biologiske **mor** på noget tidspunkt konstateret følgende sygdomme:

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:_____

2. Er der hos Deres biologiske **far** på noget tidspunkt konstateret følgende sygdomme:

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:_____

3. Er der hos Deres biologiske **søskende** på noget tidspunkt konstateret følgende sygdomme

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:_____

Kronisk obstruktiv lungesygdom i Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

PATIENT NO.:

Uddannelse og arbejde

Uddannelse

1. Hvor mange år har De gået i skole?

(sæt kryds)

1 1. 7 år eller mindre (folkeskole) ☐
1.2. 8-10 år (mellemskole, realeksamen) ☐
1.3. Over 10 år (præliminæreksamen, studentereksamen) ☐

2. Hvilken videregående uddannelse har De fået efter endt skolegang?
Vi er interesserede I uddannelsens længde, uanset om den var boglig eller praktisk.
(Hvis De har gennemgået flere uddannelser, skal De markere ved den længstvarende uddannelse)

(sæt kryds)

2.1 Ingen erhvervsuddannelse ☐
2.2 Kort videregående uddannelse, under 3 år ☐
2.3 Mellemlang videregående uddannelse, 3-4 år ☐
2.4. Lang videregående uddannelse, over 4 år ☐

Opvækst

(sæt kryds)

3.1. Er De opvokst på en gård? ☐ Nej ☐ Ja

Hvis ja
3.2. Var der husdyr på gården ☐ Nej ☐ Ja

Arbejde (hele dit arbejdsliv)

	≥20 år	19-15 år	14-10 år	9-5 år	≤ 5 år	slet ikke
4.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for støv fra planter (f.eks. halm eller træstøv) eller dyr?	☐	☐	☐	☐	☐	☐
4.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. landmand)						
Angiv max. de tre længst varende						
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐

	≥20 år	19-15 år	14-10 år	9-5 år	< 5 år	slet ikke
5.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for støv fra cement, granit, nedrivninger eller lignende?	☐	☐	☐	☐	☐	☐
5.2 Hvis De var udsat hvad var jobbet/ jobbene? (f.eks. murer)						
Angiv max. de tre længst varende						
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
6.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for røg fra smeltet metal eller svejsning?	☐	☐	☐	☐	☐	☐
6.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. svejser)						
Angiv max. de tre længst varende						
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
7.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for dampe fra malinger eller lime?	☐	☐	☐	☐	☐	☐
7.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. sprøjtemaler)						
Angiv max. de tre længst varende						
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐

Kronisk obstruktiv lungesygdom i Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

PATIENT NO.:

Rygevaner

1. Har De nogensinde røget cigaretter, cerutter, cigarer eller pibe regelmæssig, dvs. Mindst en cigaret, cerut, cigar eller et pibestop dagligt gennem et år

☐ **Nej** ☐ **Ja** **Hvis "nej", gå til side 2 "passiv rygning" (spørgsmål 11, 12 og 13)**

2. Ryger De dagligt for tiden

☐ **Nej** ☐ **Ja** **Hvis "nej", gå til "tidligere rygning"**

Nuværende rygning

3. Hvor meget ryger De dagligt? (Hvis der er tobakstyper, De ikke ryger, svares 0)

Antal	**1-5**	**6-10**	**11-15**	**16-20**	**≥ 21**
a. Antal cigaretter	☐	☐	☐	☐	☐
b. Antal cerutter	☐	☐	☐	☐	☐
c. Antal cigarer	☐	☐	☐	☐	☐
d. Antal pibestop	☐	☐	☐	☐	☐

4. Hvilken type cigaretter ryger De?

e. Mest med filter ☐
f. Mest uden filter ☐
g. Både med og uden filter ☐

5. Inhalerer De tobaksrøgen, når De ryger? (sæt en markering for hver tobakstype)

	Nej, inhalerer aldrig	Ja, lidt	Ja, dybt
h. Cigaretter	☐	☐	☐
i. Cerutter	☐	☐	☐
j. Cigarer	☐	☐	☐
k. Pibe	☐	☐	☐

Tidligere rygning

6. Hvor gammel var De, da De begyndte at ryge dagligt? _____ år

7. Hvor mange år har De i alt røget dagligt? _____ år

8. Hvor gammel var De, da De holdt op? _____ år

9. Har der siden De begyndte at ryge og inden De eventuelt holdt op sidste gang, været perioder på mere end et år, hvor De ikke har røget?

☐ Nej ☐ Ja

Hvis "ja", bedes De angive de perioder af Deres liv, hvor De ikke har røget
Fra alder ____år Til alder ____år
Fra alder ____år Til alder ____år
Fra alder ____år Til alder ____år

10. Hvor meget røg De dagligt, da De var I følgende aldersgrupper? (hvis der er tobakstyper, De ikke har røget, svares "0")

20-29 år	Antal
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pbestop	
30-39 år	
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pibestop	
40-49 år	
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pibestop	

Passiv rygning

11. Blev der røget I Deres barndomshjem?

Deres alder	**Ingen i husstanden røg**	**Én eller flere i husstanden røg**
0-9 år	☐	☐
10-19 år	☐	☐

12. Blev der røget I Deres hjem i følgende perioder af Deres liv?

Deres alder	**Ingen i husstanden røg**	**Én eller flere i husstanden røg**
20-29 år	☐	☐
30-39 år	☐	☐
40-49 år	☐	☐
50 år og indtil nu	☐	☐

13. Hvor mange timer om dagen har De gennemsnit været udsat for andres tobaksrøg på Deres arbejde I følgende perioder af Deres liv?

Deres alder	**Arbejdede ikke udenfor hjemmet**	**Antal timer udsat for andres tobaksrøg**			
		0	**1-3**	**4-7**	**8 el. flere**
Under 20 år					
20-29 år					
30-39 år					
40-49 år					
50 år indtil nu					

Kronisk obstruktiv lungesygdom I Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

PATIENT NO.:

Alkoholvaner

1. Hvor gammel var De, da De begyndte at drikke én eller flere genstande alkohol (øl, vin, hedvin eller spiritus) om måneden? (sæt kryds)

Har aldrig drukket over én genstand pr. måned	Mindre end 14 år	14-16 år	17-18 år	19-20 år	21-25 år	Over 25 år

Nuværende alkoholforbrug

2. Hvor ofte drikker De almindeligvis alkohol (øl, vin, hedvin eller spiritus)?

a.	Drikker ikke øl, vin, hedvin eller spiritus	☐ (sæt kryds)
b.	Mindre end 1 gang om måneden	☐
c.	1-3 gange om måneden	☐
d.	1 gang om ugen	☐
e.	2-4 gange om ugen	☐
f.	5-6 gange om ugen	☐
g.	Hver dag	☐

Tidligere alkoholforbrug

De følgende spørgsmål skal belyse ændringer i Deres alkoholforbrug.

3. Hvor mange genstande (øl, vin, hedvin, eller spiritus) drak De almindeligvis om ugen, da De var I følgende aldersgrupper?
Hvis der er typer af alkohol, De ikke har drukket, svares 0

Alder	Øl, ca.	Vin, ca.	Hedvin, ca.	Spiritus, ca.
20-29 år				
30-39 år				
40-49 år				
50 år indtil nu				

4. Har der, siden De begyndte at drikke alkohol været perioder på mere end et år, hvor De ikke har drukket alkohol?

☐ Nej ☐ Ja

Hvis ja, bedes De angive de perioder af Deres liv, hvor De ikke har drukket alkohol?

Periode	Fra alder	Til alder
1		
2		
3		

PATIENT NO.:

Astma og allergi

(Sæt kryds)

1. Har De nogensinde haft astma ? ☐ Nej ☐ Ja
2. Var dette bekræftet af læge? ☐ Nej ☐ Ja
3. Har De allergi i øjne eller næse (høfeber)? ☐ Nej ☐ Ja
4. Hoster De eller har De af og til problemer med vejrtrækningen om natten? ☐ Nej ☐ Ja
5. Har De af og til anfald med åndenød eller piben/hvæsen uden at have anstrengt Dem? ☐ Nej ☐ Ja
6. Hoster De I flere uger efter en almindelig forkølelse? ☐ Nej ☐ Ja
7. Får De astmamedicin, som hjælper godt på Deres gener? ☐ Nej ☐ Ja

Kronisk obstruktiv lungesygdom I Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

APPENDIX B. FOLLOW-UP DATA ESTABLISHMENT - 2008 (DANISH)

Follow-up data source from the GP examination and the participant self-administered questionnaire.

Lægeskema til KOL follow-up undersøgelse 2008.

Patientnummer: fortrykt.

Navn og CPR nummer:

Dato:

Højde:

Vægt:

Hoftemål:

Taljemål:

BT:

Resultat af spirometri:

Dette skema sendes sammen spirometrimålingen, spørgeskema, og samtykkeerklæringen til projektledelsen i vedlagte frankerede svarkuvert. Tak for hjælpen

Patientnummer: fortrykt

Sådan udfyldes skemaet
Inden De besvarer spørgsmålene, bedes De læse både spørgsmål og svar igennem. Spørgsmålene besvares ved at sætte kryds i den kasse, hvor De synes, svaret passer bedst. Sæt kun ét kryds ved hvert spørgsmål, medmindre andet er angivet.

Lungesygdomme

Nedenfor følger en række spørgsmål, hvorvidt De har haft lungesygdomme, siden De deltog i den første lungeundersøgelse.

1. Har De haft anfald af akut bronkitis siden De deltog i den første lungeundersøgelse?

Ja..... □
Nej ..... □ gå venligst til spørgsmål 5
Ved ikke .....□ gå venligst til spørgsmål 5

2. Angiv hvor mange anfald, De har haft

Antal anfald _____

3. Blev Deres akutte bronkitis bekræftet af en læge?

Ja..... □
Nej ..... □
Ved ikke .....□

4. Hvilken behandling har De modtaget for akut bronkitis?

(Gerne flere kryds)
Astmamedicin.....□
Penicillin .....□
Anden medicin ....□ angiv venligst hvilken _____
Anden behandling .....□ angiv venligst hvilken _____

5. Har De haft lungebetændelse siden De deltog i den første lungeundersøgelse?

Ja..... □
Nej ..... □ gå venligst til spørgsmål 9
Ved ikke .....□ gå venligst til spørgsmål 9

6. Angiv hvor mange gange, De har haft lungebetændelse

Antal lungebetændelser _____

7. Blev Deres lungebetændelse bekræftet af en læge?

Ja..... □
Nej ..... □
Ved ikke .....□

8. Hvilken behandling har De modtaget for lungebetændelse?

(Gerne flere kryds)
Astmamedicin.....□
Penicillin .....□
Anden medicin ....□ angiv venligst hvilken _____
Anden behandling .....□ angiv venligst hvilken _____

9. Har De haft astmaanfald siden De deltog i den første lungeundersøgelse?

Ja..... □
Nej ..... □ gå venligst til spørgsmål 13
Ved ikke .....□ gå venligst til spørgsmål 13

10. Angiv hvor mange gange, De har haft astmaanfald

Antal anfald _____

11. Blev Deres astmaanfald bekræftet af en læge?

Ja..... □
Nogle anfald .....□
Nej ..... □
Ved ikke .....□

12. Hvilken behandling har De modtaget for astma?

(Gerne flere kryds)
Astmamedicin.....□
Penicillin .....□
Anden medicin ....□ angiv venligst hvilken _____
Anden behandling .....□ angiv venligst hvilken _____

Rygning

Nedenfor følger en række spørgsmål om rygning.

13. Ryger De?
Ja..... □
Nej ..... □ gå venligst til spørgsmål 15

14. Hvor meget ryger De sædvanligvis om dagen? Angiv Deres rygning nedenfor. Gå derefter direkte til spørgsmål 16.

(Antal pr dag)
Cigaretter, antal: _____
Cigarer, antal: _____
Cerutter, antal: _____
Pibetobak, antal stop: _____

15. Har De tidligere røget?

Ja, men jeg ryger ikke længere..... □ angiv venligst årstal for hvornår De er ophørt _____

Nej ..... □ gå venligst til spørgsmål 17

16. Har De forsøgt rygestop?

Nej ..... □
Ja, enkelte gange □
Ja, adskillige gange □

Alkoholbrug

Nedenfor følger en række spørgsmål om alkoholbrug.

17. Drikker De alkohol?

Ja .....□
Nej ..... □ gå venligst til spørgsmål 19

18. Hvor meget alkohol drikker De sædvanligvis på en uge? Angiv venligst Deres alkoholbrug i skemaet nedenfor. Gå derefter direkte til spørgsmål 20.

	(Antal genstande pr uge)
Øl antal	_____
Vin, antal	_____
Hedvin, antal	_____
Spiritus, antal	_____

19. Har De nogensinde drukket alkohol?

Nej ....□
Ja, men jeg er stoppet med at drikke alkohol □
Angiv venligst årstal for, hvornår De er stoppet: _____

Arbejde

Nedenfor følger en række spørgsmål om Deres arbejdssituation, siden De deltog i den første lungeundersøgelse.

20. Er der ændringer med hensyn til Deres arbejde siden De deltog i den første lungeundersøgelse?

Ja ..... □
Nej ..... □ gå venligst til afslutning af skemaet

21. Hvornår har ændringerne fundet sted?

Årstal _____

22. Hvilke ændringer er der sket?

Jeg er ophørt med at arbejde ..... □ gå venligst til spørgsmål 23
Jeg er gået ned i arbejdstid ..... □ gå venligst til spørgsmål 23
Jeg har skiftet job ..... □ gå venligst til afslutning af skemaet
Jeg er gået op i arbejdstid ..... □ gå venligst til afslutning af skemaet
Andre ændringer ..... □ angiv venligst hvilke _____

23. Hvorfor er disse ændringer i Deres arbejdssituation sket?

Jeg er blevet pensioneret pga. alder .....□
Jeg er blevet pensioneret pga. sygdom ..... □ angiv venligst sygdom _____
Jeg er gået på efterløn .....□
Jeg er blevet afskediget ..... □
Jeg har sagt mit arbejde op ..... □
Andre årsager .....□angiv venligst årsag _____

De er velkommen til at uddybe Deres svar nedenfor. Angiv venligst numrene på de spørgsmål, De uddyber.

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____-

Vær venlig at kigge spørgeskemaet igennem for at se, om alle spørgsmål er besvaret og medbring spørgeskemaerne til undersøgelsen hos Deres læge.

MANGE TAK FOR HJÆLPEN.

APPENDIX C. SELECTED DISCO-88 CODES (DANISH)

Indtastningsmanual for spørgsmål vedr. arbejde for projektet KOL i Nordjylland og Viborg Amt

Projektleder Jens Georg Hansen

Manualen er udarbejdet af Vivi Schlünssen og Øyvind Omland. Stillingsbeskrivelser med eksponering for støv, gasser og dampe er valgt efter uafhængig score fra begge. De stillingsbeskrivelser, hvor der har været overensstemmelse er medtaget uden yderligere diskussion. Hvor der ikke har været overensstemmelse, er nogle medtaget efter en uddybende diskussion. Selve kodningen er udarbejdet på basis af Danmarks Statistiks DISCO-88, timbuktu.dst.dk/internet/NOMEN/DISCO/DISCO887.htm og Discoløn 2004, 4. udgave, Danmarks Statistik december 2003, ISBN 87-501-1366-6.

I alt er der udvalgt 72 koder for stillingsbeskrivelser, hvor det vurderes, at arbejdet kan medføre en eksponering for støv, gasser og dampe, der i karakter, intensitet og varighed kan betegnes som en mulig årsagsfaktor til KOL. Vurderingen har taget højde for ændringer i eksponeringsniveauer og har lagt vægt på historiske eksponeringsniveauer, relevant for den aktuelle alderssammensætning, for de stillingsbetegnelser, hvor der har fundet en eksponeringsreduktion sted over tid. I alt er der beskrevet 34 stillingsbeskrivelser for organisk støv, 21 for uorganisk støv, 7 for både uorganisk støv og røg, 5 for damp, 3 for røg og 2 for både organisk og uorganisk støv. Koderne ligger fra 1311 til 9330. For andre stillingsbetegnelser end dem, der er anført i manualen, foreslås anvendt 9999. Hovedparten af disse stillingsbeskrivelser ligger indenfor områderne: Ledelse (1xxx), forskning og anvendelse af færdigheder på højeste niveau inklusive undervisning (2xxx), arbejde, der forudsætter færdigheder på mellemniveau (3xxx), kontorarbejde (4xxx), salgs-, service- og omsorgsarbejde (5xxx), og militært arbejde (0xxx). Der er medtaget 8 stillingsbetegnelser indenfor disse områder (4 indenfor 1xxx, 2 indenfor 2xxx, 1 indenfor 3xxx, 1 indenfor 5xxx). De øvrige 64 findes indenfor arbejde med landbrug, gartneri, skovbrug, jagt og fiskeri (6xxx), håndværkspræget arbejde (7xxx), proces- og maskinoperatørarbejde samt transport- og anlægsarbejde (8xxx) og andet arbejde (9xxx).

Indtastningen for erhvervsspørgsmålene foreslås udført som for de øvrige spørgsmål i skemaet. De besvarelser, hvor der er usikkerhed i kodningen lægges til side og gennemgås ugentligt af en arbejdsmediciner (Vivi Schlünssen, Svend Viskum eller Øyvind Omland) med henblik på endelig kodning. Denne gennemgang og kodning kan udføres i samarbejde med Jens Georg Hansen i den udstrækning, han ønsker det. De kodede skemaer lægges til projektets sekretær til indtastning.

Århus, den 19.10.2004, Øyvind Omland

13	***Ledelse af virksomheder med færre end ti ansatte***
1311	Gård- og planteskolebestyrer (o)
1312	Bageribestyrer og systueindehaver (o)
1313	Bygmester (o)
1318	Renseriejer (d)
22	***Forskning og/eller anvendels af færdigheder indenfor medicin, farmaci og de biologiske grene af naturvidenskab.***
2213	Hortonom, landbrugskandidat, planteavlskonsulent (o)
2223	Dyrlæge (o)
322	***Assistentarbejde indenfor sundhedssektoren***
3227	Kennelassistent, veterinærsygeplejerske (o)
516	***Overvågnings- og redningsarbejde***
5161	Brandmand, røgdykker (r)
611	***Arbejde vedrørende plantevækst***
6111	Markarbejder i landbruget (o)
612	***Arbejde med dyr***
6121	Staldarbejder i landbruget (o)
6122	Fjerkræavler, ægproducent (o)
6129	Minkfarmer (o)
613	***Arbejde med såvel markafgrøder som husdyr***
6130	Landmand, landbrugsmedhjælper (o)
614	***Arbejde indenfor skovbrug***
6141	Skovløber, plantør (o)
711	***Mine- og stenhuggerarbejde***
7111	Minearbejder (u)
7113	Stenhugger (u)
712	***Bygningsarbejde (basis)***
7121	Tagtækker (u)
7122	Murer, flisemester (u)
7123	Terrassoarbejder, struktør (u)
7124	Tømrer, snedker, bådebygger (o)
713	***Bygningsarbejde (finish)***
7131	Tagdækker (u)
7132	Gulvafhøvler, gulvlægger (o)
7133	Stukkatør (u)
7134	Isolatør (u)
714	***Maler, tapetsererarbejde m.v.***
7141	Maler, skibsmaler, skiltemaler (d)
7142	Sprøjte-, autolakerer (d)
7143	Skorstensfejer (o)

72	***Metal- og maskinarbejde***
7211	Former, Støber (u)
7212	Svejser (r)
7213	Karosseribygger, kedel-, kobber-, pladesmed (u, r)
7214	Skibsbygger, stålmester (u, r)
7215	Rigger (u, r)
722	***Grovsmede-, værktøjsmagerarbejde***
7224	Metalsliber (u)
741	***Arbejde indenfor nærings- og nydelsesmiddelindustrien***
7411	Røgemester (r)
7412	Bager (o)
7416	Cigarmager, tobakssorterer (o)
742	***Arbejde indenfor træindustrien***
7421	Træimprægneringsarbejder (o)
7423	Maskindrejer, trædrejer (o)
811	***Mine- og mineraludvindingsanlægsarbejde***
8111	Borer (u)
8112	Mineral- og stenbrudsanlægsarbejder (u)
8113	Driller, borepladsarbejder (u)
812	***Jern-, metalværkds- og støberianlægsarebjde***
8121	Stålarbejder (u, r)
8122	Smelter (u, r)
8123	Støberiarbejder (u, r)
813	***Glas-, keramik- og teglprocesanlægsarbejde***
8131	Ovnarbejder, teglværksarbejder (u, r)
814	***Træ- og papirprocesanlægsarbejde***
8141	Finerarbejder, savskærer (o)
8143	Papirarbejder (o)
815	***Kemisk procesanlægsarbejde***
8151	Elementstøber, knusemester (u)
8152	Lakkoger (d)
821	***Betjening af maskiner indenfor metal- og mineralindustrien***
8212	Betonblander, cementarbejder (u)
822	***Betjening af maskiner indenfor den kemiske industri***
8222	Ammunitionsarbejder (u)
8223	Industrilakerer (d)
824	***Betjening af maskiner indenfor træindustrien***
8240	Savværksarbejder, træarbejder (o)

825	***Betjening af maskiner indenfor den grafiske industri og papirvareindustrien***
8252	Bogbinderassistent (o)
8253	Papirvarearbejder, æskearbejder (o)
826	***Betjening af maskiner indenfor tekstil-, skind- og lædervareindustrien***
8261	Karter, spinder, spoler (o)
827	***Betjening af maskiner indenfor nærings- og nydelsesmiddelindustrien***
8273	Møller, mølleriarbejder (o)
8274	Bageriarbejder, bageriassistent (o)
8276	Sukkerarbejder (o)
8277	Kaffebrænder (o)
8279	Cigaretarbejder, skråtobaksspinder (o)
828	***Monterings- og samlebåndsarbejde***
8285	Finersamler, møbelbehandler (o)
833	***Arbejde med andre mobile maskiner og køretøjer***
8331	Traktorfører (o, u)
8332	Maskinfører, gravemester (o, u)
916	***Renovations- og gadefejerarbejde***
9161	Renovationsarbejder (o)
9162	Gadefejer (u)
92	***Medhjælp indenfor landbrug, gartneri, fiskeri og skovbrug***
9211	Landbrugs- og gartnerimedhjælper (o)
9212	Skovhugger, plantagearbejder (o)
931	***Manuelt arbejde indenfor bygge- og anlægssektoren***
9311	Grusgravarbejder (u)
9312	Asfaltarbejder, vejarbejder (u, d, r)
9313	Murerarbejdsmand, bygningsarbejder (u)
933	***Manuel transport- og lagerarbejde***
9330	Havnearbejder, lagerarbejder og læssemand (u)

o = organisk støv
u = uorganisk støv
r = røg
d = damp

APPENDIX D. APPLIED DISCO-88 CODES AND CORRESPONDING OCCUPATIONAL ANSWERS (DANISH)

APPENDIX D.1: DISCO-88 koder indenfor organisk støv (org) eksponering

Koder	• **Udvalgte koder: 34 (org), 2 (org + inorg)** • **Anvendte koder: 27 (org) – se nedenfor** • **Ikke anvendte koder:** • **7 (org): 1312, 7132, 7421, 8141, 8252, 8274, 8276** • **2 (org + inorg): 8331, 8332**

DISCO	Spørgeskema tekst
1311	• Planteskoleejer • Selvstændig gartneriejer • Selvstændig: frugt, grønt, blomster
1313	• Bygmester • Entreprenør, formand • Tilsynsførende på byggepladser • Tømrer – byggemester
2213	• Landbrugsuddannelse, konsulent (frøavl) • Svinekonsulent • Zoologisk konservator
2223	• Dyrlæge • Embedsdyrlæge • Praktiserende dyrlæge
3227	• Dyrehandel • Hundepension
6111	• (Landbrug) – gartneri • Anlægsgartner • Arbejdsmand – gødningsstøv • Frugtavler • Gartner • Gartner, jernvare, møbelfabrik (også kodet: svejser, sprøjtemaler) • Gartneri • Gartneri medhjælper • Gartneri, landbrug • Gartneriuddannelse • Halm • Halm, træstøv • Halmvarmeværk-fliseværk • Kabelgravning • Kartoffelsorterer • Køre halm ind + fyre med halm 3-5 gange daglig • Landmand-traktorfører • Maskinstation • Medarbejdende hustru i planteskole • Medhjælp i gartneri • Meje ved landbrug • Mejetærskefører • Planteskole • Planteskolegartner • Støv fra halm • Ufaglært gartner • Varmemester (brændsel-halm)
6121	• 1 år som medhjælp i stald • 200+ privat dyr/fuglehold • Arbejde i svinestald • Arbejder med heste • Dyr • Dyr – grise, heste • Dyr, halm

	• Dyr, halm, høstøv • Halm, dyr • Halm, hø, ridelærer, foderstoffer • Halm, korn, køer, grise • Halm, træstøv, dyr • Hesteavl • Hesteopdræt • Hestepasser • Hestestald • Hjalp til i stalden • Husdyr • Inseminør • Kostaldmedhjælper • Kreatur • Kvæg, svin, halm • Køer og svin • Landbrug m husdyr • Landmand - haft hest • Landmand med kvæg • Medhjælper i stald • Opvokset på gård, i stald, egen gård med dyr • Svin • Svineavl • Svinefodermester • Svinestald • Svinestald som svinefodermester/ driftsleder
6122	• Hønsefarm • Hønseri • Kyllingefarm • Kyllinger • Pasning af fjerkræ
6129	• Medhjælp i minkfarm • Mink • Mink i fritiden • Minkavler • Minkfarm • Pelsdyr • Pelsdyravler • Pelsdyravler, træstøv 1 mdr årlig i 53 år

6130	• Arbejde på ægtefælles gård • Arbejdet og boet på en gård • Arbejdet på gården • Boede og arbejde i fritiden på et husmandssted • Bonde • Deltaget i landbrug hele livet • Deltidslandmand • Fodermester • Foderstof og landbrug • Folkeskolelærer/hobby landmand • Fritidslandmand • Fåreavler • Gedefarm • Hobbylandbrug • Landbrug • Landbruget • Landbrugsdrift • Landbrugsmedhjælper, hustru • Landmand • Landmand – delvis • Landmand + rengøring • Landmand og minkavler • Landmand, arbejdsmand, murer, sømand, lastbilchauffør • Landmand, chauffør, lagermand • Landmand, chauffør, reder • Landmand, chauffør, slagteriarbejder • Landmand, gartner • Landmand, graver • Landmand, grønttørreri • Landmand, industri træ • Landmand, kommunalarbejder

	• Landmand, maskin…, teglværk • Landmand, maskinstation • Landmand, mekaniker • Landmand, savskærer, buschauffør • Landmand, savværksarbejde • Landmand, specialarbejder på træ/møbelfabrik • Landmand, svin og slagte kyllinger • Landmand, traktorfører • Landmand, tømrer-bygningsarbejder • Landmand, vicevært • Landmand, vognmand (dyr, briketter) • Lidt landbrug • Maskinstation/landbrug • Medhjælpende hustru i landbrug • Medhjælpende hustru på gård • Medhjælpende hustru til landmand • Medhjælper landbrug, gift med landmand • Selvstændig landmand
6141	• Skovbrug • Skovbruger
7124	• Bygningssnedker / tømrer • Forskallingstømrer • I lære som snedker • Læretid som tømrer • Møbelsnedker • Skibssnedker • Skibstømrer • Snedker • Snedker (møbel) • Snedker/lakerer
	• Snedker/møbelfabrikant • Snedkeri • Træstøv - tømrer/snedker • Træstøv under mesterlære som karetmager/tømrer • Tømrer • Tømrer (byggeplads, værksted) • Tømrer asbestplader • Tømrer samt skibstømrer • Tømrer/bygningsarbejder • Tømrer/snedker • Tømrerlærling • Tømrersvend • Tømrervirksomhed • Tømrerværksted
7143	• Skorstensfejer
7412	• Bager • Bager (melstøv) • Bagerkone • Bageri • Bagersvend • Mel • Pakkeri brødfabrik
7416	• Cigarmager/ snusblanding
7423	• Bødker
8143	• Papirmølle
8240	• Arbejde på spånpladefabrik • Brændselarbejder • Højtaler – støv fra finer og spånplader • Maskinsnedker • Møbelfabrik • Møbelfabriksarbejder • Møbelindustriarbejder • Møbelindustrien • Møbel-maskinsnedkeri • Møbelproduktion • Savfører • Savskærer

	• Savværk • Savværk, trævarefabrik, plast, smedeværksted • Savværksarbejder • Specialarbejder i træindustri (pudse-/slibearbejde) • Træfabrik • Træindustri • Træindustri lager og chauffør • Træindustri lak-lim • Træstøv • Trævarefabrik • Tømrer arbejder på en køkkenfabrik
8253	• Bates ventil sække, Nørresundby • Kartonnage
8261	• Arbejde med huder og skind • Buntmager • Dynefabrik, fjer • Fabrik - syerske • Fabrik konfektion • Fiberstøv fra tøj • Konfektionsindustri • Lædervarefabrik - tilskærer • Modist • Møbelpolster • Møbelpolstring, hund • Rebslageri • Syerske • Systue • Sækkefabrik • Tekstilarbejde • Tekstilfabrik • Tekstilforædling • Tekstilindustri • Tekstilmedarbejder • Tilskærer • Væver
8273	• …foderstof

	• …formaling af korn og mel • Foderfabrik • Foderstof • Foderstof, mølleri • Foderstoffabrik • Foderstoffer • Foderstoffirma • Frørenseri • Korn • Korn og foderstoffer • Kornbehandlingsanlæg • Kornfoderfirma • Kornlager • Kornstøv • Korntørreri • Lagerarbejde korn/foderstof • Lagerarbejder (foderstof) • Lagermand – korn • Læreplads med foderstof og brændsel • Lærling korn og foderstoffer • Mølleri • Mølleri – korn og mel • På mølle (kornstøv) • Solsikkeskrå, pakhuse foderstof • Svinefoder
8277	• Kaffe – rå
8279	• Cigarmager • CV Obel • Skandinavisk tobak • Tobaksarbejde • Tobaksfabrik • Tobaksstøv • Tobaksstøv, maskinarbejder
8285	• Træ/finer
9161	• Renovationsarbejder
9211	• Alt-mulig-mand på gård • Ansat på en gård • Arbejde for bønder

	• Arbejdede på gårde, kvæghaller, kornmagasiner • Arbejdet med landbrug • Arbejdet på landet • Arbejdsmand på gård • Boet og arbejdet på gård • Gårdskarl • Hjalp i landbruget • Hjalp på gården • Hjalp til på en gård • Hjalp til på gården • Karl på gård • Landarbejder • Landbrug hos forældre (22-27 + 33-40 år) • Landbrug/maskinstation • Landbrugsarbejder • Landbrugselev • Landbrugsmedarbejder og gartneriarbejder • Landbrugsmedarbejder, fodermester • Landbrugsmedhjælper • Landmand, arbejdsmand • Landmandsarbejde • Landmandselev • Markarbejde, arbejde i svinestald • Maskinarbejde, passet køer, passet grise • Medhjælp på gård • Medhjælper på forældres gård • Medhjælper på fædrene gård • Opvokset og arbejde på landet • Opvokset og tjente på landet • Passe dyr, høste • Praktisk landbrugsuddannelse • Tjeneste på landet

	• Tjenestekarl på landet • Tjente på en gård • Ungmedhjælper i landbrug • Var på en gård • Ved landbruget • Vindumovergård Gods
9212	• Delvis skovarbejde 6' mand • Skov • Skovarbejde • Skovarbejder

APPENDIX D.2: DISCO-88 koder indenfor uorganisk støv (inorg) eksponering

Koder	• **Udvalgte koder: 20 (inorg), 2 (org + inorg), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Anvendte koder: 12 (inorg), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Ikke anvendte koder:** • **8 (inorg): 7121, 7123, 7133, 8111, 8113, 8151, 8222, 9162** • **2 (org + inorg): 8331, 8332**

DISCO	Spørgeskema tekst
7111	• Stenkulmine
7113	• Stenbrud • Stenhugning • Stenhugger (60er)
7122	• Murer • Murer/murerlærling • Murersvend
7131	• Tagdækker (asfalt) • Arbejdsmand, tagdækker, chauffør
7134	• Arbejdsmand/isolatør • Isolationsarbejde (asbest) • Isolatør • Isolatør stenuld/glasuld • Isolering • Isolering, tagplader • Rockuld ved smelteovne • Rockwool
7211	• Blystøber til akkumulator • Former • Letmetalstøbning – former
7213	• Alt-mulig-mand hos
+ røg	smed • Arbejdede som 'smededreng' (+ malede med maling og celluloselak) • Arbejdsmand v. vand og gasmester • Automekaniker, pladesmed • Autopladeværksted • Blikkenslager • Blikkenslager, asbest, isolering • Blikkenslager/svejser • Grav og blogsmed • Grovsmed, svejser • Karosseri arbejde – slibning • Kedelsmed • Klejnsmed • Klejnsmed, smed i byggesektor, smed foderstoffabrik • Landbrugsmaskinsmed • Landbrugssmed • Landsbysmed • Maskinarbejder/smed • Metaludstansning på svejsefabrik • Pladesmed • Pladesmed/autolakering • Pladesmed/beholder • Reparationer v landbruget, støv fra vinkelsliber, maskinarbejder, sprøjtemaling af maskiner (tolket som landbrugsmaskinsmed) • Rørlægger • Rørlægger i skibsværft og offshore industri

	• Rørsmed • Sanitet • Smed • Smed – VVS • Smed og svejser • Smed på betonstøberi • Smed/montør • Smed/reparatør cementfabrik • Smed/svejse • Smede og maskinarbejder • Smedearbejde • Smedearbejde (minus svejsning) • Smedearbejde og svejsning • Smedearbejdsmand • Smedelærling • Smedemedhjælper • Smedeværksted • Smedeværksted i røg og os • Smedje • Svejser + kedelsmed • Svejser, smed • Uddannet smed, daglig svejserøg • Vogn og beslagsmed • VVS • VVS blikkenslager • VVS mand • VVS montør
7214 + røg	• Arbejdsmand (værft) • Arbejdsmand i støven på B&W • Skibsbyg arb…. • Skibsbygger • Skibsbygger på værftet • Skibsværft • Slibning af glasfiber • Svejsning inde/ude på skib • Værft

	• Værft arbejde
7215 + røg	• Rigger
7224	• Barberbladefabrik (slibestøv) • Metalsliber • Slibearbejde ved værft • Slibning af biler • Stålborde + slibning • Svejsning, metalslibning • Svejsning/slibning • Værktøjsmager • Værktøjsslibning
8112	• Jernmalm • Molerarbejder • Molerindustri, jord, kloak, beton arb, stenhugning • Stenknuser • Stenknusermaskine • Stenknusning
8121 + røg	• Metal drejer • Metalarbejde • Skrot • Specialarbejder på beholder fabrik (jern) • Stålværkstedsarbejde
8122 + røg	• Blysmeltning • Jernkogeri • Metal smeltning (bly) • Metalsmelter • Smeltet metal • Smeltning af bly
8123 + røg	• Arbejde med og smeltning af bly • Arbejde på jernstøberi • Blystøv • Dania • Former/støber i metal • Håndformer/jernstøberi + metal • Jernstøberi • Jernstøv

	• Jernværk • Kernemager • Lejestøber • Metalstøberi • Renser på metalstøberi • Støber på jernstøberi • Støberi • Støberi – metal • Støberiarbejde • Støbning metal • Svejser + jernstøberi • Svejsning af zink og galvanisering • Svejsning og galvanisering • Svejsning, jernstøberi, metalstøberi • Svejsning, metalstøbning
8131 + røg	• Arbejde på teglværk • Brander teglværk, jord og beton arbejder, landmand • Kedelpasser • Sod fra kedelrensning • Teglværk • Teglværker • Teglværksarbejde • Teglværksarbejder • Udsat for ler og glasstøv som pottemager
8212	• Arbejde med eternit • Arbejder inden for cement industrien • Arbejdet med asbeststøv i perioder • Arbejdsmand eternit/Aalborg Portland • Asbest • Asbeststøv • Asbeststøv, isoleringsstøv • Beton/elementfabrik • Betonarbejder • Betonfabrik

	• Betonindustri • Bådsmand i Aalborg Portland (nok båndsmand…) • Cement • Cement, granit, nedrivning • Cementarbejde • Cementfabrik • Cementformand • Cementindustri • Cementstøber • Cementstøber beton • Cementstøberi • Cementstøv • Cementvarefabrik • Cementvareindustri • Dansk eternitfabrik • Eternit/cement • Eternitarbejder • Eternitstøv (asbest) • Flisefabrik • Flyveaske, støv • Formalet flyveaske • Glasfiber – asbest • Industri – asbest • Kalkværker • Medhjælper cementstøv • Roteroven, cementmølle, Aalborg Portland • Rørdal • Støbearbejder (uspecificeret jern/cement) • Støber (også kodet: betonfabrik)
9311	• Grusgrav
9312 + røg + dampe	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og

	dieselos)
9313	• Altmuligmand v entreprenør • Arbejdsmand, murer, isolatør • Betonfabrik/ murerarbejde • Bygge og anlæg • Byggeri anlæg • Bygningsarbejde • Bygningshåndværker • Entreprenør • Entreprenør (dræning) • Entreprenørarbejde • Entreprenørarbejde/ nedbrydningsarbejde • Gasbetonmontør • Jord og beton • Jord og betonarbejder • Landbrugsentreprenør • Murer (også kodet: tømrer) • Murer og tømrer • Murer/betonarbejder nedrivningsarbejde • Murer/nedrydning • Murerarbejder • Murerarbejdsmand • Murerarbejdsmand, isoleringsarbejder – rockwool og glasuld • Murermedhjælper • Mureroppasser • Murstøv • Nedbryder • Nedbrydningsarbejde, entreprenørarbejde, betonstøv • Nedrivning af lejligheder, murer, mv • Nedrivning og opbygning • Nedrivning/husbyggeri • Ombygning og

	nybygning af boliger mm • Sandblæser • Sandblæsning, cementarbejde, stenknusemaskine • Specialarbejder anlæg og byg
9330	• Havnearbejder • I 25 år – dagligt fejet i lagerhallen hvor jeg arbejdede • Lagerarbejde - betonstøv • Lagerarbejder på Sadolin malerfabrik • Lagermand • Lagermedarbejder

APPENDIX D.3: DISCO-88 koder indenfor røg (fume) eksponering

Koder	• **Udvalgte koder: 3 (fume), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Anvendte koder: 2 (fume), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Ikke anvendt kode: 1 (fume): 7411**

DISCO	Spørgeskema tekst
5161	• Brandmand
7212	• Akkumulator svejser • Aluminium svejsning • CO2 - svejsning • Elektronik loddearbejde • Fabrik – svejser • Fabrik metalsvejser • Håndlodning • Lodde blykabler • Lodde komponenter som radioarbejde • Loddearbejde • Loddedame • Loddede i flydende loddetin • Loddepige på B&O • Lodning • Lodning (slag) • Lodning af elektronik • Lodning af printplader • Lodning i elektronikindustrien • Lodning på fabrik • Maskinarbejder og svejser • Maskinarbejder/VVS/ isolering/svejsning/ mekaniker (også kodet: landmand) • Maskinoperatør, svejser ved siden af • Metalstøberi/svejsning • Montrice (loddearbejde) • Pressvejsning • Punktsvejsning • Rørsvejsning • Skærebrænding • Skæreolie – svejsning • Smed (svejser) • Svejsearbejde • Svejseos • Svejser • Svejser – acetone • Svejser – metalstøv • Svejser – rørmager • Svejser m. svejsetråd • Svejser og maskinarbejder • Svejser, maskinist • Svejser, skibsbygger • Svejser, skærebrænder • Svejser/mekaniker • Svejser/rørlægger • Svejser/smed • Svejserøg • Svejsning • Svejsning (aluminium), maskinarbejde • Svejsning af rustfrit stål • Svejsning og lign ved reparation af landbrugsmaskiner • Svejsning, fabrik • Tinlodning • TV lodning
7213 + uorg	• Alt-mulig-mand hos smed • Arbejdede som ’smededreng’ (+ malede med maling og celluloselak) • Arbejdsmand v. vand og gasmester

	• Automekaniker, pladesmed • Autopladeværksted • Blikkenslager • Blikkenslager, asbest, isolering • Blikkenslager/svejser • Grav og blogsmed • Grovsmed, svejser • Karosseri arbejde – slibning • Kedelsmed • Klejnsmed • Klejnsmed, smed i byggesektor, smed foderstoffabrik • Landbrugsmaskinsmed • Landbrugssmed • Landsbysmed • Maskinarbejder/smed • Metaludstansning på svejsefabrik • Pladesmed • Pladesmed/autolakering • Pladesmed/beholder • Reparationer v landbruget, støv fra vinkelsliber, maskinarbejder, sprøjtemaling af maskiner (tolket som landbrugsmaskinsmed) • Rørlægger • Rørlægger i skibsværft og offshore industri • Rørsmed • Sanitet • Smed • Smed – VVS • Smed og svejser • Smed på betonstøberi • Smed/montør • Smed/reparatør cementfabrik

	• Smed/svejse • Smede og maskinarbejder • Smedearbejde • Smedearbejde (minus svejsning) • Smedearbejde og svejsning • Smedearbejdsmand • Smedelærling • Smedemedhjælper • Smedeværksted • Smedeværksted i røg og os • Smedje • Svejser + kedelsmed • Svejser, smed • Uddannet smed, daglig svejserøg • Vogn og beslagsmed • VVS • VVS blikkenslager • VVS mand • VVS montør
7214 + uorg	• Arbejdsmand (værft) • Arbejdsmand i støven på B&W • Skibsbyg arb…. • Skibsbygger • Skibsbygger på værftet • Skibsværft • Slibning af glasfiber • Svejsning inde/ude på skib • Værft • Værft arbejde
7215 + uorg	• Rigger
8121 + uorg	• Metal drejer • Metalarbejde • Skrot • Specialarbejder på beholder fabrik (jern) • Stålværkstedsarbejde

8122 + uorg	• Blysmeltning • Jernkogeri • Metal smeltning (bly) • Metalsmelter • Smeltet metal • Smeltning af bly
8123 + uorg	• Arbejde med og smeltning af bly • Arbejde på jernstøberi • Blystøv • Dania • Former/støber i metal • Håndformer/jernstøberi + metal • Jernstøberi • Jernstøv • Jernværk • Kernemager • Lejestøber • Metalstøberi • Renser på metalstøberi • Støber på jernstøberi • Støberi • Støberi – metal • Støberiarbejde • Støbning metal • Svejser + jernstøberi • Svejsning af zink og galvanisering • Svejsning og galvanisering • Svejsning, jernstøberi, metalstøberi • Svejsning, metalstøbning
8131 + uorg	• Arbejde på teglværk • Brander teglværk, jord og beton arbejder, landmand
	• Kedelpasser • Sod fra kedelrensning • Teglværk • Teglværker • Teglværksarbejde • Teglværksarbejder • Udsat for ler og glasstøv som pottemager
9312 + uorg + dampe	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og dieselos)

APPENDIX D.4: DISCO-88 koder indenfor damp (vapour) eksponering

Koder	• **Udvalgte koder: 5 (vapour), 1 (inorg + fume + vapour)** • **Anvendte koder: 5 (vapour), 1 (inorg + fume + vapour)**

DISCO	Spørgeskema tekst
1318	• Renseri
7141	• Bygningsmaler • Deltidsmaler • Glasfiber og acetone, maling • Glasfiber/maling • Glasmaler • Gulvlakering • Maler • Malerdampe • Malersvend • Malerværksted • Maling • Maling og stenolie • Skibsmaler • Skibsmaling • Tagmaler
7142	• Autolakerer • Autolakering • Automaler • Billakering • Epoxy • Epoxymaler, borerig, Norge • Hjælpe sprøjtemaler • Industrimaler • Lakerer • Lakering • Maling, epoxy, polyester • Sprøjte og bygningsmaler • Sprøjtekabinemaler, epoxy • Sprøjtemaler • Sprøjtemaler, arbejde med fortynder og triklor
	• Sprøjteværksted (lak) • Tæppelakering • Undervognsbehandling • Undervognsbehandling af biler • Varm lakering af motorer
8152	• Afrenset metaldele med rensevæske • Bejdsning/afsyring af jern (syrebade) • Dampe – farvninger • Galvanisering • Glasur og begitning af lervarer • Kemisk tøjrensning
8223	• Glasfiberarbejde • Gummifabrik • Industrilakering • Lakering af mobiler • Lakering fabrik • Lystryk (ammoniak-dampe) • Polyester/glasfiber • Rensning af genbrugsgiftflasker • Reparationsarbejde/ limning af glasfiber • Vulkanisør
9312 +uorg +røg	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og • dieselos)

APPENDIX E. PAPER I

Occupational chronic obstructive pulmonary disease in a Danish population-based study

Else Toft Würtz, Vivi Schlünssen, Tine Halsen Malling, Jens Georg Hansen, Øyvind Omland

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ORIGINAL RESEARCH

Occupational Chronic Obstructive Pulmonary Disease in a Danish Population-Based Study

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Abstract

The aim was to explore the impact of occupation on chronic obstructive pulmonary disease (COPD) in a cross-sectional population-based study among subjects aged 45 to 84 years. In a stratified sampling 89 general practitioners practices (GPP) in Denmark recruited 3106 males and 1636 females through the Danish Civil Registration System. COPD was defined by spirometry by the 2.5th-centile Lower Limit of Normal of FEV_1 and FEV_1/FVC. Information about smoking, occupational exposure and the respective occupations were obtained from questionnaires. Occupations followed the Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88). Exposure to vapour, gas, dust (organic and inorganic), and fume (VGDF) in each occupation (yes/no) was evaluated by two independent specialist in occupational medicine. Exposures were divided in no, low, medium, and high exposure as 0, <5, 5–14, and ≥ 15 years in the job, respectively. Data was analysed by a mixed random effect logistic regression model. The age-standardised COPD study prevalence was 5.0%. Of 372 DISCO-88 codes 72 were identified with relevant exposure to VGDF. 46% of the participants reported at least one occupation with VGDF exposure. Adjusted for smoking, age, sex, and GPP a dose-dependent association of COPD was found among workers in jobs with high organic dust exposure, with OR 1.56 (95% CI 1.09–2.24). Restricted to agriculture the OR was 1.59 (95% CI: 1.08–2.33). No association was observed for workers in jobs with inorganic dust, fume/gas, or vapour exposures. In summary, occupational organic dust exposure was associated to the prevalence of COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common and widespread disease (1,2), with a wide range of co-morbidities (3). In the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (1) COPD is ranked as 7th in disability-adjusted life years (DALY) in Western Europe. Smoking is the major risk factor for COPD, but worldwide, up to half of COPD cases are in fact due to nonsmoking causes, e.g., exposure to biomass smoke; occupational exposure to vapour, gases, dust and fumes (VGDF); history of pulmonary tuberculosis or chronic asthma; outdoor air pollution, and poor socioeconomic status (4). Growing evidence suggests that about 15% of COPD could be attributable to occupational exposure (5–7). Currently available treatments have minimal impact on progression of the disease (8) so attempts to prevent COPD are attractive and favourable, and occupational exposures can be prevented or reduced in many trades. The aim of the present study was to estimate the occupational contribution to the risk of COPD in a cross-sectional population-based Danish study of 45–84-year-old participants.

Keywords: epidemiology, occupational exposure, organic dust, prevalence study

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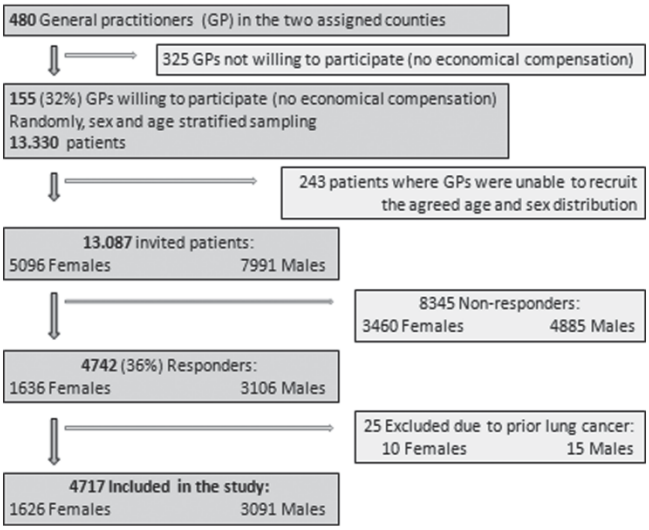

Figure 1. Flow chart of the study enrolment population.

Methods

Population

The study is based on baseline data from the North Jutland COPD Prevention Study (NCPS) from 2004 (9). The population was selected from two former counties in Denmark (North Jutland and Viborg) with together 299,000 inhabitants aged 45–84 years (January 2005). In Denmark all citizens have free access to medical care provided by a general practitioner. All 480 general practitioners (GP) in the two counties were invited to participate, Figure 1 (Flow chart). The study recruited patients from 155 GP situated in 89 practices (GPP). The Danish individual personal 10-digit Civil Registration System was used to select a randomly, but age and sex stratified sample of persons aged 45–84 with an overweight group of elderly and men, based on the expected Danish prevalence of COPD in 10-year groups (10).

The selected subjects received an invitation by mail in which they were requested to contact their general practitioner in order to participate in the study. The participants consisted of a mixed urban/rural population. In the period October 2004– September 2006, in all 4742 (36%) of the invited 13,087 persons entered the study, and consulted their general practitioner. Applied baseline data consisted of a self-administered questionnaire including a question of prior asthma; "Have you ever had asthma?" (Yes/No), spirometry tests, height and age. Participants with a prior lung cancer were excluded (n = 25), leaving 4717 participants for analysis in the current study.

Spirometry

Pulmonary function tests by spirometry [forced expiratory volume per second (FEV_1) and forced vital capacity (FVC)], were performed by the general practitioner or a trained member of the practice staff with the general practitioners own spirometer. Volume and time calibration of the spirometers was performed before study start and every six months by trained staff using a one litre syringe. Adequate spirometry test instructions followed the statement from The European Respiratory Society (ERS) (11) and the standard from The American Thoracic Society (ATS) (12). For participants with a FEV_1/FVC ratio below 0.70 a reversibility test was performed with eight inhalations of Combivent (1 dose = 100 µg salbutamol and 20 µg ipratropium) and spirometry test was assessed after 30 min. The reference population used was The Global Lung Function 2012 equations (13) in the "GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3" (14), which takes age, sex and race-ethnicity into account to estimate the subsequent applied z-scores.

COPD

We defined COPD by lung function measurements according to the method of Lower Limit of Normal (LLN) for FEV_1/FVC, as recommended by the ATS and ERS (15), and used the GLI-2012 prediction equations (13). In a screening setting of normal subjects the LLN is the 2.5th-centile (z-score = –1.96). To distinguish a group of more severe airways obstruction we also added the screening criterion of the LLN for FEV_1 of a z-score = –2.0 as recommended by Quanjer et al. (16). COPD

defined by LLN was estimated using the prebronchodilator values. Prevalence data was additionally presented based on the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria with a fixed FEV_1/FVC ratio < 0.70 and FEV_1 < 80% of the predicted value (moderate airways obstruction; GOLD 2+) (3). COPD defined by GOLD was estimated using the postbronchodilator values if prebronchodilator FEV_1/FVC ratio was < 0.70 otherwise prebronchodilator values were used.

Occupational exposure assessment

The occupational exposure assessment was based on a self-administered questionnaire, where the participants were asked for duration of exposure (5-year span) to organic dust, inorganic dust, fume/gas, and vapour, respectively. Furthermore, for each exposure type the participants could state up to three job titles and appertaining durations (5-year span). Where exposure to dust, gas, vapours or fumes were known to be present occupational codes were selected from the Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) (17) by two specialists in occupational medicine. Final decision was agreed upon by the two specialists.

For each of the exposure agents, the total period of employment was calculated by adding the mean years from each 5-year span of each stated employment. The total duration of employment per exposure was then calculated to define four categories of cumulated duration of exposure: no exposure (0 years), low exposure (<5 years), medium exposure (5–14), and high exposure (≥15 years). When summarising the four exposures in one overall VGDF occupational exposure, the "low exposure" was defined to have specific low exposures only, "medium exposure" to have specific medium exposure but no high exposures, and finally "high exposure" to have any specific high exposure.

Smoking habits

From the questionnaire three different smoking variables were estimated, i.e, status (never, ever or current smoking), duration (years) and cumulated smoking as pack-years: ((number of cigarettes smoked per day × number of years smoked)/20). Different types of smoking were transformed to cigarettes by the following equations: one cheroot = three cigarettes; one cigar = four cigarettes, one pipe bowl = three cigarettes. Pack-years were reduced to three categories: below 10, 10–20, and above 20 pack-years, respectively.

Statistics

The chi-square test for categorical variables was used to assess differences between sub-groups of the study population. The COPD prevalence was age-standardised to the Danish population, January 2006. Univariate and mixed random effect logistic regression model (18) with GPP as random variable was used to estimate the association between COPD and occupational exposures with adjustment for pack-year, sex and age as fixed effects, and likelihood ratio tests for interaction. The McNemar test for matched data was used to compare the two methods of assessing COPD; LLN and GOLD as defined earlier. Sensitivity analyses were performed by recoding all the missing occupational exposures (i) into no exposure and (ii) into high exposure, or by (iii) excluding all participants with prior self-reported asthma. The 95% confidence intervals (CI) were calculated using a normal approximation. The significance level was set at 5%. Statistical analyses were conducted in Stata12.1 (StataCorp LP, 2011).

Ethics

The NCPS-study has been performed in accordance to the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

Results

Occupational exposure

Of the existing 372 DISCO-88 codes 72 were considered by the two specialists to include relevant exposure to VGDF. In the study population 27 of the 34 selected DISCO-88 codes with relevant exposure to organic dust were identified, likewise12 of 20 to inorganic dust, 2 of 3 to fume/gas, 5 of 5 to vapour, 7 of 7 to inorganic dust and fume/gas, 0 of 2 to organic and inorganic dust, and 1 of 1 to inorganic dust, fume/gas and vapour (Documented in the supplementary Table S1). About half of the population, 49%, reported no DISCO-88 code with relevant exposure, 31% reported one DISCO-88 code with relevant exposure, and 15% (n = 693) reported between two and six DISCO-88 codes with relevant exposures, while 5% did not answer the occupational question. The occupational exposures are separately illustrated by sex and level of exposure in Figure 2. Figure 2 underlines the fact that many participants (15%), especially the men, have several exposures. The exposure pillars in the figure section with VGDF are less than the sum of the specific exposure pillars.

An overview of the age distribution, occupational exposures and smoking habits is given by sex in Table 1. The majority of women (81%) had no relevant exposure to VGDF, while 40% of the men had a relevant high exposure to VGDF. Organic dust was the most frequent occupational exposure in both men (56%) and women (19%). A considerable number of men were also relevant exposed to other agents: Inorganic dust 24%, fume/gas 16% and vapour 6%. Overall, 23% of all subjects were current smokers and 43% were ex-smokers. Men were somewhat more likely than women to be ex-smokers ($p < 0.001$), whereas never smokers were more prevalent among women ($p < 0.001$). The mean smoking duration and number of pack-years were significantly higher in men compared to women ($p < 0.001$).

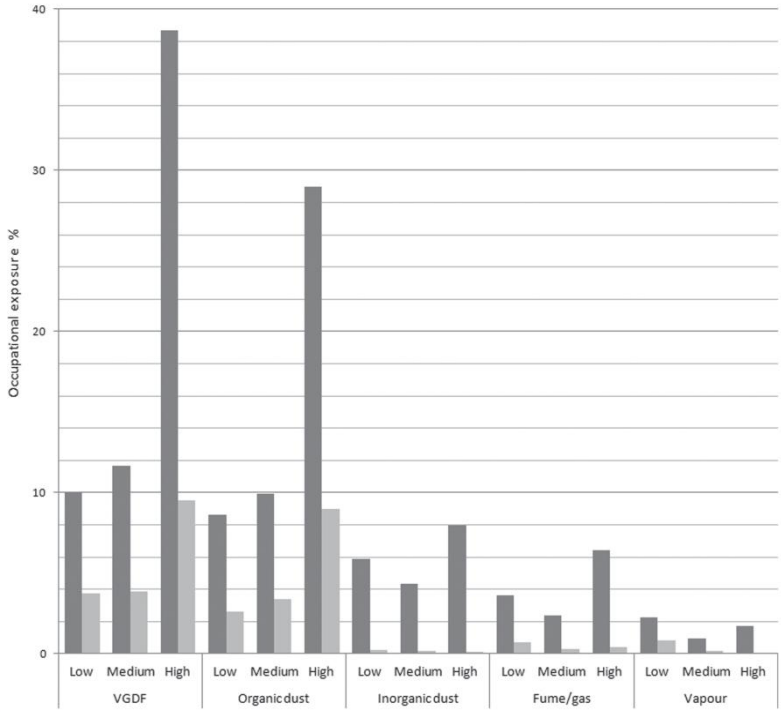

Figure 2. Occupational exposure in males (■) and females (■) (N = 4717). Vapour, Gas, Dust and/or Fume (VGDF) exposure: Low, "Only having specific low exposure"; Medium, "Having specific medium exposure but no specific high exposure"; and High, "Having any specific high exposure" Organic dust, inorganic dust, fume/gas and vapours occupational exposure means of duration: Low, <5 years in exposed job (excluding no exposure); Medium, 5–14 years in exposed job; and High, ≥15 years in exposed job.

Prevalence of COPD

Twenty participants either missed (n = 2), were incapable of accomplishing (n = 12) or had an insufficiently performed spirometry test (n = 6), leaving 4697 with a prebronchodilator spirometry, and 726 also had a postbronchodilator spirometry. Table 2 stratifies the cases by sex and age, and according to the LLN 2.5th centile method the overall study prevalence of COPD was 5.9% (n = 279), and when age-standardised to the Danish population 5.0%. The study prevalence among never smokers was 1.7% (n = 26).

The GOLD 2+ COPD prevalence was also estimated: A postbronchodilator spirometry was conducted in 726 (77%) of the 949 participants with a prebronchodilator FEV_1/FVC ratio < 0.70. For the GOLD definition of COPD the remaining 223 with a prebronchodilator $FEV_1/FVC < 0.70$ and no reversibility test were excluded. The excluded subjects were by prebronchodilator lung function test distributed as: COPD by GOLD n = 119, and COPD by LLN n = 32 (discordance n = 87). The overall study prevalence of GOLD 2+ COPD was 8.6% (n = 386), and 6.8% when age-standardised to the Danish population.

In a paired comparison between the two criteria for defining COPD there was a significant difference both overall and when stratified by sex, $p < 0.001$. Table 3 display the overall comparison, with 173 discordant diagnoses between the LLN and GOLD definitions.

Occupational exposures and COPD (LLN)

The results from the univariate and multiple regression analyses on the association between occupational VGDF exposure, organic dust exposure, and COPD are shown in Table 4. In the VGDF analysis an association between COPD and occupational exposure was indicated. The odds ratio (OR) decreased from crude to adjusted (ORadj) (pack-years, age group, sex and GPP), but was still significant in the medium exposed group, ORadj 1.61 (95% CI: 1.03–2.51) and also the trend analysis maintained significance, $p < 0.05$.

Table 1. Description of the study population, N = 4717

	Female		Male		Total	
Characteristic	n	(%)	n	(%)	n	(%)
Age						
Age groups						
45–54 years	509	(31)	400	(13)	909	(19)
55–64 years	420	(26)	649	(21)	1069	(23)
65–74 years	426	(26)	1359	(44)	1785	(38)
75–84 years	271	(17)	683	(22)	954	(20)
Total	1626		3091		4717	
Mean age (SD)	*62.4*	*(10.8)*	*67.0*	*(9.3)*	*65.5*	*(10.1)*
Occupational exposure						
VGDF duration of occupational exposure (n = 4474)						
No exposure	1226	(81)	1104	(37)	2330	(52)
Only low[a] exposures	61	(4)	309	(10)	370	(8)
Medium[b] exposure (and no high)	63	(4)	360	(12)	423	(9)
Any high[c] exposure	155	(10)	1196	(40)	1351	(30)
Any organic dust (n = 3883)	244	(19)	1469	(56)	1713	(44)
Any inorganic dust (n = 3776)	9	(1)	563	(24)	572	(15)
Any fume/gas (n = 3826)	23	(2)	384	(16)	407	(11)
Any vapour (n = 3701)	17	(1)	152	(6)	169	(5)
Smoking habits						
Status (n = 4692)						
Never smokers	722	(45)	853	(28)	1575	(34)
Ex-smokers	537	(33)	1490	(48)	2027	(43)
Current smokers	354	(22)	736	(24)	1090	(23)
Duration (n = 4614)						
Mean smoked years (SD)	*15.4*	*(17.9)*	*25.5*	*(20.8)*	*22.0*	*(20.4)*
Cumulated smoking (n = 4371)						
Mean smoked pack-years (SD)	*8.7*	*(12.7)*	*26.0*	*(29.8)*	*20.1*	*(26.6)*

[a]Low: Exposure but < 5 years.
[b]Medium: 5 to 14 years of exposure.
[c]High: ≥15 years of exposure.
VGDF: Vapour, gas, dust and fume.
SD: Standard deviation.
All variables between sexes, $p < 0.001$.

Table 2. The study and age-standardised prevalence of COPD by sex and age group (n = 4697)

	COPD defined by LLN[a]								
	Female			Male			Total		
	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)
Age groups									
45–54	17	3.4	(1.8–4.9)	13	3.3	(1.5–5.0)	30	3.3	(2.1–4.5)
55–64	18	4.3	(2.4–6.3)	26	4.0	(2.5–5.5)	44	4.1	(2.9–5.3)
65–74	21	5.0	(2.9–7.0)	105	7.8	(6.3–9.2)	126	7.1	(5.9–8.3)
75–84	20	7.5	(4.3–10.6)	59	8.7	(6.6–10.8)	79	8.3	(6.6–10.1)
All ages	76	4.7	(3.7–5.7)	203	6.6	(5.7–7.5)	279	5.9	(5.3–6.6)
Age-standardised[b]		4.6	(4.6–4.6)		5.0	(5.0–5.0)		5.0	(5.0–5.0)

COPD: Chronic Obstructive Pulmonary Disease.
CI: Confidence Interval.
[a]LLN: Lower Limit of Normal; FEV_1/FVC z-score <−1.96 and FEV_1 z-score <−2.0.
[b]Prevalence age-standardised to the Danish population, January 2006.

Table 3. Comparison of LLN and GOLD methods to define COPD by spirometry in the study population

		GOLD		
		Normal or GOLD I	GOLD II or more severe[a]	Total
LLN	Normal or mild COPD	4071	156	4227
	Moderate or more severe[b]	17	230	247
Total		4088	386	4474

LLN: Lower Limit of Normal.
GOLD: Global Initiative for Chronic Obstructive Lung Diseases.
COPD: Chronic Obstructive Pulmonary Disease.
[a]FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value.
[b]FEV_1/FVC z-score <−1.96 and FEV_1 z-score <−2.0.

Looking at the different categories of occupational exposure the ORadj for high organic dust exposure was associated to COPD and the trend in ORadjs was significant; 1.56 (95% CI: 1.09–2.24), p < 0.02, respectively.

Excluding participants with prior asthma (n = 497) reduced the high exposure association and trend of occupational organic dust exposure to COPD into insignificance, ORadj 1.47 (0.92–2.34), p = 0.15, respectively. Restricting the analysis to patients with mild COPD and probably vague or no symptoms slightly increased the association between high organic dust exposure and COPD, ORadj 1.88 (1.13–3.13). Two main exposure groups were identified in the organic occupational dust exposure; Agriculture as the main group followed by "wood" (timber industry and carpenters). Of a total of 1926 reports agriculture was reported 1495 times (78%) and "wood" 289 times (15%). When the analysis was restricted to agriculture alone ORadj and trend remained significant; 1.59 (95% CI: 1.08–2.33), p < 0.02, respectively.

Although no evidence of associations was seen in the smaller 'wood' group of timber industry and carpenters. Specific inorganic dust, fume/gas and vapour occupational exposures showed no trend or evidence for an association with COPD, data not shown. Sensitivity analyses related to the multiple regression analysis of the VGDF exposure and COPD added 198 participants with missing occupational exposure to no exposure. The medium exposure and trend changed to borderline significance, ORadj 1.55 (95% CI: 1.00–2.41) p = 0.05 and p = 0.06, respectively. When adding the 723 participants with missing occupational organic dust exposure to the unexposed the high exposure estimate became insignificant in the sensitivity analyses of organic dust; both as ORadj (1.30 (95% CI: 0.93–1.80)) and in the trend analysis (p = 0.15).

Discussion

In this study we found a LLN defined age-standardised prevalence of COPD of 5.0%. Occupational organic dust exposure was in a dose-dependent manner associated to the prevalence of COPD.

Table 4. Occupational and covariates associations to COPD in the population-based study.

	Odds Ratio (OR)			
	Crude		Adjusted[a]	
	OR	95% CI	OR	95% CI
VGDF occupational exposure	n = 4457		n = 4132	
No	1.00	Reference	1.00	Reference
Low	1.08	(0.66–1.78)	1.05	(0.61–1.80)
Medium	**1.87**	**(1.27–2.77)**	**1.61**	**(1.03–2.51)**
High	**1.55**	**(1.17–2.05)**	1.38	(0.99–1.93)
Score test for trend		**p < 0.001**		**p = 0.031[b]**
Covariates				
<10 pack-years			1.00	Reference
10–20 pack-years			**2.60**	**(1.54–4.38)**
>20 pack-years			**7.26**	**(4.95–10.66)**
Age 45–54			1.00	Reference
Age 55–64			1.22	(0.73–2.02)
Age 65–74			**2.09**	**(1.33–3.29)**
Age 75–84			**2.28**	**(1.38–3.76)**
Males			1.00	Reference
Females			**1.78**	**(1.24–2.56)**
Organic dust exposure	n = 3867		n = 3607	
No	1.00	Reference	1.00	Reference
Low	1.22	(0.73–2.05)	1.15	(0.65–2.03)
Medium	1.49	(0.95–2.33)	1.24	(0.74–2.07)
High	**1.50**	**(1.10–2.04)**	**1.56**	**(1.09–2.24)**
Score test for trend		**p = 0.006**		**p = 0.017[b]**
Covariates				
<10 pack-years			1.00	Reference
10–20 pack-years			**2.36**	**(1.34–4.16)**
>20 pack-years			**6.82**	**(4.55–10.22)**
Age 45–54			1.00	Reference
Age 55–64			1.23	(0.71–2.14)
Age 65–74			**2.10**	**(1.28–3.44)**
Age 75–84			**2.13**	**(1.23–3.69)**
Males			1.00	Reference
Females			**1.89**	**(1.30–2.77)**

COPD: Chronic Obstructive Pulmonary Disease.
CI: Confidence Interval.
VGDF: Vapour, gas, dust and fume.
Bold estimates: Beyond the significance level of 5%.
[a]Random effect logistic regression adjusted for; Pack-year group: < 10, 10–20, and > 20 smoked pack-years; Age group: 45–54, 55–64, 65–74, 75–84 years of age; Sex; General practitioner practice (random variable).
[b]Without the random variable.

COPD

In epidemiologic studies the definition of disease is often simplified and not identical with the corresponding clinical diagnose. We defined COPD by lung function measurements. The LLN approach is recommended

concurrently by the ERS and ATS (15). As opposed to the GOLD fixed method, which is somewhat biased by participants age, sex and height (19), the LLN definition ensures that the participants do have a degree of airflow obstruction outside accepted population norms. However, the 2.5th centile as a diagnostic criterion is a conservative approach, aiming to minimize the percentage of false positives at the expense of an increased number of false negatives.

Furthermore, COPD severity described in the ATS/ERS recommendation utilise the fixed FEV_1 percent predicted (15). In the present study we have analysed the data based on Quanjer et al. (16). They have recently recommended a new grading of the obstructive lung disease that is clinically relevant and free of biases related to age, height, sex and ethnic group (16). Adding the restriction of FEV_1 z-score <–2 we obtain a group of subjects having moderate airways obstruction, corresponding to the ATS/ERS moderate airways obstruction (16).

Measuring COPD or asthma

The 1993 official statement from ERS (11) and the 2005 ATS/ERS standardisation of lung function testing (15) do not judge a significant positive bronchodilator response to differentiate between asthma and COPD in similar ways. Furthermore, there is no evidence to clearly differentiate asthma and COPD patients by bronchodilator response (15). The response to bronchodilators varies within and between individuals (20) and when predicted reference values were established as prebronchodilator values, this lead to some overestimation of the reversibility of a low FEV_1/FVC ratio. In this study asthma was managed in sensitivity analyses by excluding participants with self-reported prior asthma.

Despite that asthma predisposes to the development of COPD (21,22) excluding these subjects from the analysis might underestimate the true association to occupation as an inclusion of the subjects is likely to overestimate the association. The best estimate might therefore be in-between these ORs.

Occupational exposure assessment

The occupational exposures were assessed by a self-administered questionnaire on exposures and occupation validated with an expert judgement. This approach is considered more sound than questionnaires alone (23), and our results support that the often used self-reported exposures might be prone to bias. This or similar combined approaches is well established and have been utilized in several population-based retrospective studies (24–26). Recall bias of occupational exposure might be introduced tending to overestimate the association between exposure and disease, although the risk was considered low, as the questionnaires were filled out before the GP examination, and thus only participants with well known COPD, might have been more aware of job exposures.

As patients with mild COPD have no symptoms, this assumption was tested by estimating the association of mild COPD and high organic dust exposure, which slightly increased the OR. This result support that our findings is not skewed by recall bias. Further, few Danes aged 45 to 84 have knowledge of an association between occupational exposure to VGDF and COPD, and the a priori selected DISCO-88 codes and expert management of each job title into DISCO-88, without awareness of COPD status, have further blinded the exposure assessment.

Smoking assessment

No common conversion of different types of smoking to amount of cigarettes were found (e.g. from the ERS). The utilised equations are clinically used at Aalborg University Hospital, Denmark and nearly the same as Bernaards et al. used in a comparison study of calculating pack-years prospectively and retrospectively (27).

Prevalence

The COPD prevalence's estimated in this study, i.e. an age-standardised prevalence of 5.0% are in accordance with other studies from Europe and US where the prevalence is reported to be between 4.5 and 10% using different diagnostic criteria (24, 28–31). We have taken a conservative approach with the FEV_1/FVC LLN of 2.5th centile instead of the clinical used 5th centile to reflect a screening setting. This approach gives rise to more false negative and less false positive subjects. Using the clinical FEV_1/FVC<LLN 5th centile (z-score < –1.64) and FEV_1 < LLN –2 the age-standardised prevalence was 5.9% (n = 329). As expected the GOLD 2+ prevalence was lower in this study compared to the prior NCPS article estimating the GOLD 1+ prevalence (9) on the same data.

Occupational exposure association to COPD

A novel review by Omland et al. (32) identified 29 former population-based studies of occupational exposure to VGDF and COPD, restricting inclusion in their analysis to studies that have used ATS/ERS approved spirometric criteria for defining abnormalities in airflow obstruction and level of FEV_1 (15). There were differences in associations and exposures in the included studies, but only two with a nonsignificant association both carried out in younger populations (33,34). The present study found positive associations within the organic occupational exposure, maybe reflecting the dominating position of agriculture in Northern Denmark as the major occupation for exposure to VGDF in the study.

Associations were similar when restricting the analysis from organic dust exposure to agriculture exposure alone. Several cross-sectional studies have found an association between occupational organic dust exposure in agriculture and COPD (35–37). We found a weaker association between high organic dust exposure and COPD when excluding subjects with prior self-reported

history of asthma OR 1.47 (0.92–2.34), trend p = 0.15. In the SAPALDIA study, only including nonasthmatics, the incidence rate ratio was 2.76 (95% CI: 1.32–5.75) with any organic dust exposure in ever-smokers and COPD (38). The differences in observation might be due to difference in the concentration of the exposure, low statistical power in our study or may reflect healthy-worker selection where subjects with possible prior asthma leave farming to more manageable jobs with lower occupational exposures. These associations should be addressed in prevention of new cases and deterioration of working cases.

Strengths and limitations

The limited reduction of OR in the sensitivity analyses of the high organic exposure emphasises the occupational association, although the associations become insignificant. The external study validity is considered to be high in a Western world setting with similar occupational distribution, due to expected similar occupational exposures. The enrolled study population included more young women and fewer participants in the oldest group than among nonresponders. This might introduce an age-dependent healthier study population tending to underestimate the associations. Spirometry error measurements have been managed by regular calibration, but the variations of brands among GPP were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements as recommended by the ERS and the ATS (15).

Possible misclassifications would be of nondifferential nature and tend to underestimate the associations. Moreover, when using a spirometrically defined COPD, some COPD patients with compliance difficulties might be excluded from the analysis resulting in false low associations. Information bias of exposure was reduced by using the specialist-assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. A validation of the self-reported exposures showed that job titles were often stated within the wrong exposure and, furthermore, the specialists assessed many of the job titles as having no occupational exposure.

Conclusion

In this population-based study involving 4697 subjects we found an age-standardised prevalence of COPD of 5.0%. Organic dust exposure was in a dose-dependent manner associated to the prevalence of COPD, independent of smoking habits, although the study found no associations to other less-common exposures.

Declaration of Interest Statement

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary materials are available in the online version of this article.

Online supplementary material

Title
Occupational chronic obstructive pulmonary disease in a Danish population-based study

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Supplementary Table S1

The a priori 72 selected Disco-88 codes with known relevant occupational exposure to organic dust, inorganic dust, fume/gas, and vapour.

Job description[a]	Unit group[a]			Assigned exposure			
	ISCO-88	ISCO-88 (COM)	DISCO-88	Organic dust	Inorganic dust	Fume/gas	Vapour
General managers in agriculture, hunting, forestry and fishing	1311	1311	1311	X			
General managers in manufacturing	1312	1312	1312	(X)			
General managers in construction	1313	1313	1313	X			
General managers in personal care, cleaning and related services	1318	1318	1318				X
Agronomists and related professionals	2213	2213	2213	X			
Veterinarians	2223	2223	2223	X			
Veterinary assistants	3227	3227	3227	X			
Fire-fighters	5161	5161	5161			X	
Field crop and vegetable growers	6111	6111	6111	X			
Dairy and livestock producers	6121	6121	6121	X			
Poultry producers	6122	6122	6122	X			
Market-oriented animal producers and related workers not elsewhere classified	6129	6129	6129	X			
Market-oriented crop and animal producers	6130	6130	6130	X			
Forestry workers and loggers	6141	6141	6141	X			
Miners and quarry workers	7111	7111	7111		X		
Stone splitters, cutters and carvers	7113	7113	7113		X		
Builders, traditional materials	7121	7121	7121		(X)		
Bricklayers and stonemasons	7122	7122	7122		X		
Concrete placers, concrete finishers and related workers	7123	7123	7123		(X)		
Carpenters and joiners	7124	7124	7124	X			
Roofers	7131	7131	7131		X		
Floor layers and tile setters	7132	7132	7132	(X)			
Plasterers	7133	7133	7133		(X)		
Insulation workers	7134	7134	7134		X		
Painters and related workers	7141	7141	7141				X
Varnishers and related painters	7142	-	7142				X
Building structure cleaners	7143	7143	7143	X			
Metal moulders and coremakers	7211	7211	7211		X		
Welders and flamecutters	7212	7212	7212			X	

Job description[a]	Unit group[a]			Assigned exposure			
	ISCO-88	ISCO-88 (COM)	DISCO-88	Organic dust	Inorganic dust	Fume/gas	Vapour
Sheet-metal workers	7213	7213	7213		X	X	
Structural-metal preparers and erectors	7214	7214	7214		X	X	
Riggers and cable splicers	7215	7215	7215		X	X	
Metal wheel-grinders, polishers and tool sharpeners	7224	7224	7224		X		
Butchers, fishmongers and related food preparers	7411	7411	7411			(X)	
Bakers, pastry-cooks and confectione-ry makers	7412	7412	7412	X			
Tobacco preparers and tobacco products makers	7416	7416	7416	X			
Wood treaters	7421	7421	7421	(X)			
Woodworking-machine setters and setter-operators	7423	7423	7423	X			
Mining-plant operators	8111	8111	8111		(X)		
Mineral-ore- and stone-processing-plant operators	8112	8112	8112		X		
Well drillers and borers and related workers	8113	8113	8113		(X)		
Ore and metal furnace operators	8121	8121	8121		X	X	
Metal melters, casters and rolling-mill operators	8122	8122	8122		X	X	
Metal-heat-treating-plant operators	8123	8123	8123		X	X	
Glass and ceramics kiln and related machine operators	8131	8131	8131		X	X	
Wood-processing-plant operators	8141	8141	8141	(X)			
Papermaking-plant operators	8143	8143	8143	X			
Crushing-, grinding- and chemical-mixing-machinery operators	8151	8151	8151		(X)		
Chemical-heat-treating-plant operators	8152	8152	8152				X
Cement and other mineral products machine operators	8212	8212	8212		X		
Ammunition- and explosive-products machine operators	8222	8222	8222		(X)		
Metal finishing-, plating- and coating-machine operators	8223	8223	8223				X
Wood-products machine operators	8240	8240	8240	X			
Bookbinding-machine operators	8252	8252	8252	(X)			
Paper-products machine operators	8253	8253	8253	X			
Fibre-preparing-, spinning- and winding-machine operators	8261	8261	8261	X			
Grain- and spice-milling-machine operators	8273	8273	8273	X			
Baked-goods, cereal and chocolate-products machine operators	8274	8274	8274	(X)			
Sugar production machine operators	8276	8276	8276	(X)			
Tea-, coffee-, and cocoa-processing-machine operators	8277	8277	8277	X			

Job description[a]	Unit group[a]			Assigned exposure			
	ISCO-88	ISCO-88 (COM)	DISCO-88	Organic dust	Inorganic dust	Fume/gas	Vapour
Tobacco production machine operators	8279	8279	8279	X			
Wood and related products assemblers	8285	8285	8285	X			
Motorised farm and forestry plant operators	8331	8331	8331	(X)	(X)		
Earth-moving- and related plant operators	8332	8332	8332	(X)	(X)		
Garbage collectors	9161	9161	9161	X			
Sweepers and related labourers	9162	9162	9162		(X)		
Farm-hands and labourers	9211	9211	9211	X			
Forestry labourers	9212	9212	9212	X			
Mining and quarrying labourers	9311	9311	9311		X		
Construction and maintenance labourers: roads, dams and similar constructions	9312	9312	9312		X	X	X
Building construction labourers	9313	9313	9313		X		
Transport labourers and freight handlers	-	9330	9330		X		
Number of assigned codes			72	X: 27 (X): 9	X: 20 (X): 10	X: 10 (X): 1	X: 6 (X): 0

ISCO-88: The International Standard Classification of Occupations, revision 1988

ISCO-88 (COM): The European Union variant of ISCO-88

DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988

(X): Assigned exposure codes, but not applied in this study population

[a] Statistics Denmark (3 April, 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx

APPENDIX F. PAPER II

Occupational chronic obstructive pulmonary disease among Danish women: a population-based cross-sectional study

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Submitted

ABSTRACT

BACKGROUND: Few studies have focused on occupational COPD in women. We have analysed cross-sectional data among 1626 Danish women aged 45-84.

METHODS: In 2004-06 participants were recruited from 155 general practitioners (GP) in Denmark. The women accounted for 39% of the age and sex stratified sampling. COPD was defined as FEV_1/ FVC z-score <2 standard deviations and FEV_1 z-score <2. Smoking habits and occupational history was obtained by questionnaire. The Danish version of The International Standard Classification of Occupations (DISCO-88) and expert derived assessment was used to select jobs with exposure to vapour, gas, dust (organic/inorganic), and fume (VGDF). Smoking was grouped in 0-<10, 10-20, and >20 smoked pack-years.

RESULTS: Of 372 DISCO-88 codes 72 were identified with VGDF exposure. Occupational exposure to VGDF were stated by 17% of the women (n=279). Organic dust exposure was the dominating exposure (83%). The age-standardised COPD prevalence was 4.6% (n=76). Exposures were dichotomised as ever or never exposed subjects. In a mixed model adjusting for smoking, age and GP practice an increased risk of COPD was found for subjects exposed to VGDF OR 1.98 (95% CI 1.06-3.69) and organic dust OR 2.05 (95% CI 1.04-4.08). Excluding 174 with prior asthma increased both associations; VGDF OR 2.81 (95% CI 1.36-5.79) and organic dust OR 2.99 (95% CI 1.37-6.55). The study population attributable fraction for the proportion of COPD due to occupational VGDF/organic dust exposure was 14/15%.

CONCLUSION: The risk for COPD was increased among women exposed to occupational VGDF and organic dust.

BACKGROUND

Women are more prone to develop COPD compared to men with similar exposures, and this has been ascribed to different susceptibility to tobacco, and anatomic, hormonal and behavioural differences [1, 2]. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 [3] the age-standardised COPD among women is globally ranked as the 10th frequent cause of disability-adjusted life years (DALY), 11th in Western Europe and 4th in Denmark [4]. Smoking is the major risk factor for COPD, but worldwide, up to half of COPD cases are in fact due to non-smoking causes e.g.: exposure to biomass smoke; occupational exposure to vapour, gases, dust and fumes (VGDF); history of pulmonary tuberculosis or chronic asthma; outdoor air pollution, and poor socioeconomic status [5]. Furthermore, women have a different clinical expression of COPD compared to men [6-8] with different prevalence across countries [9]. Growing evidence suggests that the population attributable fraction (PAF) for the proportion of COPD due to occupational VGDF exposure is about 15% [10-13], but no estimates solely among older women have as far as we are aware of been published. Currently available treatments have minimal impact on progression of the disease [14] so attempts to prevent COPD are urgent and favourable, and occupational exposures can be eliminated or reduced in many trades. Despite these finding few studies have focused on the occupational exposure as a risk factor for COPD in women. We have therefore analysed the occupational contribution to COPD in a cross-sectional population-based Danish study of women aged 45 to 84 years.

MATERIALS AND METHODS

Population

The study is based on baseline data from the North Jutland COPD Prevention Study (NCPS) from 2004 [15]. The population was selected from two former counties in Denmark (North Jutland and Viborg) with a mixed urban/rural population and approximately 153,000 female inhabitants aged 45-84 years (January 2005). In Denmark all citizens have free access to medical care provided by a general practitioner (GP). All 480 GP in the two counties were invited to participate. The study recruited patients from 155 GP situated in 89 practices (GPP). The Danish individual personal 10-digit Civil Registration System (CPR) was used to select a randomly, but age and sex stratified sample, of which the women accounted for 39% [15]. The stratified sampling was based on the expected Danish prevalence of COPD in 10-year groups [16]. The selected subjects received a mailed invitation letter requesting them to contact their general practitioner for participating in the study. In the period October 2004 - September 2006, in all 1636 (32%) of the invited 5096 women entered the study, and consulted their GP. Applied baseline data consisted of a self-administered questionnaire including a question of prior asthma; “Have you ever had asthma?” (Yes/No), spirometry tests, height and age.

Participants with a prior lung cancer were excluded (n=10), leaving 1626 women for analysis in the current study.

Spirometry

The pulmonary function tests by spirometry (forced expiratory volume per second (FEV_1) and forced vital capacity (FVC)), were performed by the general practitioner or a trained member of the practice staff using the general practitioners own spirometer. Volume and time calibration of the spirometers was performed before study start and every six months by trained staff using a one litre syringe. Adequate spirometry test instructions followed the statement from The European Respiratory Society (ERS) [17] and the standard from The American Thoracic Society (ATS) [18]. For participants with a FEV_1/FVC ratio below 0.70 a reversibility test was performed with eight inhalations of Combivent (1 dose=100 µg salbutamol and 20 µg ipratropium) and spirometry test was assessed after 30 minutes. The reference population used was The Global Lung Function 2012 Equations [19] in the "GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3" [20] which takes age, sex and race-ethnicity into account for estimating the subsequent applied z-scores.

COPD

We defined COPD by employing the method of Lower Limit of Normal (LLN) for FEV_1/FVC, as recommended by the ATS and ERS [21], using the GLI-2012 prediction equations [19]. In a screening setting of normal subjects the LLN is the 2.5th centile (z-score = -1.96). To distinguish a group of more severe airways obstruction we also added the screening criterion of the LLN for FEV_1 of a z-score = -2.0 as recommended by Quanjer et al [22]. COPD defined by LLN was estimated using the pre bronchodilator values. Prevalence data was additionally presented based on the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria with a fixed FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value (moderate airways obstruction; GOLD 2+) [23]. COPD defined by GOLD was estimated using the post bronchodilator values if pre bronchodilator FEV_1/FVC ratio was <0.70 otherwise pre bronchodilator values were used.

Occupational exposure assessment

The occupational exposure assessment was based on a self-administered questionnaire, where the participants were asked for duration of exposure (five year span) to organic dust, inorganic dust, fume/gas, and vapour, respectively. Furthermore, for each exposure type the participants could state up to three job titles and appertaining durations (five years span). Occupational codes where exposure to VGDF was known to be present were a priori selected from the Danish adaptation of The International Standard Classification of Occupations, revision

1988 (DISCO-88) [24] by two specialists in occupational medicine. Exposure due to job titles stated by the participants was validated and final decision was agreed upon by the two specialists. For each of the exposure agents, the total period of employment was calculated by adding the mean in each span of employment. The total duration of employment per exposure was then calculated to define four categories of cumulated duration of exposure: no exposure (0 years), low exposure (<5 years), medium exposure (5-14), and high exposure (≥15 years). When summarising the four exposures in one overall VGDF occupational exposure, the "low exposure" was defined as having specific low exposures only, "medium exposure" as having specific medium exposure but no high exposures, and finally "high exposure" as having any specific high exposure.

Smoking habits

From the questionnaire the cumulated smoking as pack-years was estimated: ((number of cigarettes smoked per day × number of years smoked)/20). Different types of smoking were transformed to cigarettes by the following equations: one cheroot=three cigarettes; one cigar=four cigarettes, one pipe bowl=three cigarettes. Pack-years were reduced to three categories: below 10, 10-20, and above 20 pack-years, respectively.

Statistics

The chi-square test for categorical variables was used to assess differences between sub-groups of the study population. The COPD prevalence was age-standardised to the Danish population, January 2006. A mixed random effect logistic regression model [25] with GPP as random variable was used to estimate the association between COPD and occupational exposures with adjustment for pack-year and age. The McNemar test for matched data was used to compare the two methods of assessing COPD; LLN and GOLD. Sensitivity analyses were performed by (i) excluding all participants with self-reported asthma and (ii) include mild COPD in the LLN COPD definition (FEV_1/FVC 2.5th centile, but not the FEV_1 LLN criteria) and (iii) exclude women with a tentative exposure. The PAF was estimated as the proportion of cases exposed*(OR-1)/OR (OR: odds ratio) [26]. The 95% confidence intervals (CI) were calculated using a normal approximation. The significance level was set at 5%. Statistical analyses were conducted in Stata12.1 (StataCorp LP, 2011).

Ethics

The NCPS-study has been performed in accordance with the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

RESULTS

Occupational exposure

Of the existing 372 DISCO-88 codes 72 were considered by the two specialists to include relevant exposure to VGDF. Of the 72 selected DISCO-88 codes 25 (35%) were identified in this female study population, illustrated by occupational exposure (Figure 1).

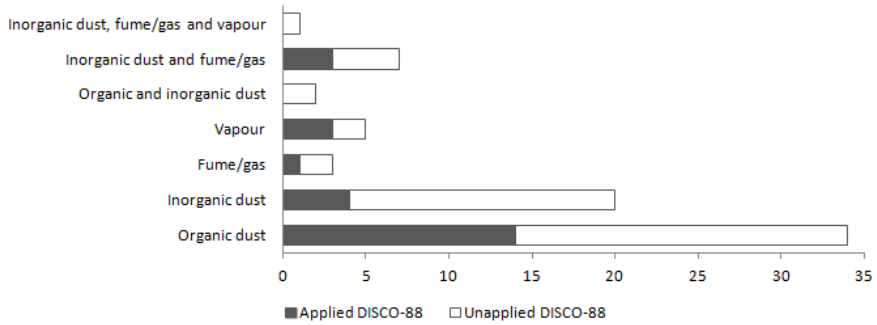

Figure 1 The assigned occupational exposure of the 72 selected DISCO-88 codes in the study.
Abbreviation: DISCO-88, the Danish adaptation of The International Standard Classification of Occupations, revision 1988.

Three quarters of the women reported no DISCO-88 code with relevant exposure, 15% reported one DISCO-88 code with relevant exposure, and 2% reported two or three DISCO-88 codes with relevant exposures, while 7% (n=121) didn't answer the occupational questions. This corresponds to 279 women with a relevant occupational exposure. An overview of the age distribution, smoking habits, and prior asthma is given in Table 1. No difference was estimated between smoking status and number of exposed jobs, p=0.47, nor smoking status and number of exposure agents (VGDF), p=0.22. The percentages with the occupational exposures are illustrated by exposure (Figure 2). Organic dust was the most frequent occupational exposure among the women (15%), and accounted for 83% of all exposures.

Table 1

Description of the study population by smoked pack-years, N=1626*

	Smoked pack years							
	Never smokers		1<10		10-20		>20	
Characteristic	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Agegroups								
45 - 54 years	216	(30)	93	(35)	83	(34)	88	(32)
55 - 64 years	193	(27)	60	(22)	73	(30)	71	(26)
65 - 74 years	192	(27)	61	(23)	55	(23)	81	(30)
75 - 84 years	121	(17)	55	(20)	31	(13)	31	(11)
Total	722	(44)	269	(17)	242	(15)	271	(17)
Mean age (SD)	*62.7*	*(10.8)*	*62.6*	*(11.3)*	*60.8*	*(10.5)*	*61.6*	*(10.0)*
Smoking duration								
Mean smoked years (SD)	-	-	*16.0*	*(10.6)*	*32.7*	*(10.3)*	*39.9*	*(9.4)*
Prior asthma	78	(11)	22	(8)	19	(8)	42	(15)

SD: Standard deviation. *Missing pack-year information, n=122 (8%)

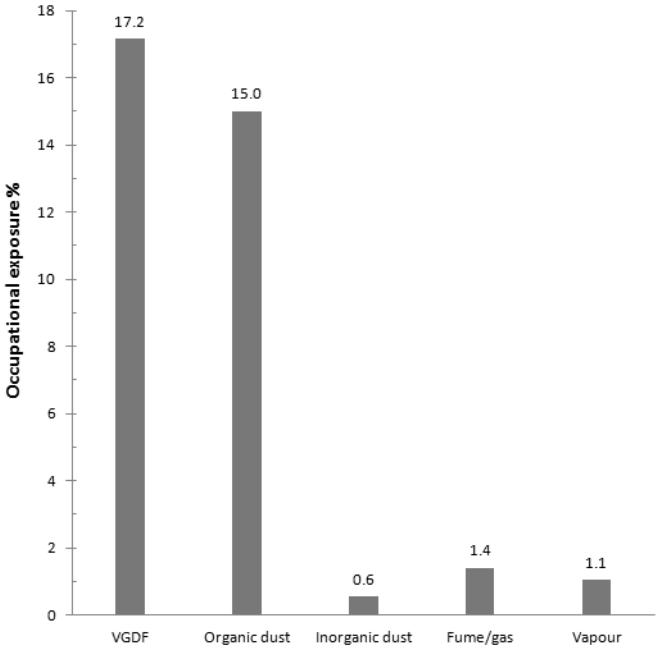

Figure 2 Percentages with any occupational exposure in different categories, N=1626.
Abbreviation: VGDF, vapour, gas, dust and/or fume.

Prevalence of COPD

Nine participants either missed (n=1), were incapable of accomplishing (n=6) or had an insufficiently performed spirometry test (n=2), leaving 1617 with a pre bronchodilator spirometry. According to the LLN 2.5th centile method (FEV_1/FVC and FEV_1) the study prevalence of at least moderate COPD was 4.7% (n=76), and when age-standardised to the Danish population 4.6%.

The GOLD 2+ COPD prevalence was also estimated: A post bronchodilator spirometry was conducted in 164 (71%) of the 230 participants with a pre bronchodilator FEV_1/FVC ratio <0.70. For the GOLD definition of COPD the remaining 66 were excluded. The study prevalence of GOLD 2+ COPD was 5.7% (n=88), and 5.5% when age-standardised to the Danish population.

In a paired comparison between the two criteria for defining COPD there was, a significant difference in the oldest age group (75-84 years) where more subjects had COPD using the GOLD definition (15.3%) compared to the LLN definition (7.5%), p<0.001.

Occupational exposures and COPD (LLN)

Trend analyses showed a dose-response association between VGDF or organic dust exposure and COPD when adjusted for pack-years in relation to the no, low, medium and high exposures, both p=0.02. Due to power considerations (mainly few exposed women) the exposures were dichotomised as never or ever exposed subjects. The results from the univariate and mixed model regression analyses on the association between occupational VGDF, organic dust exposure, and COPD are shown in Table 2.

Table 2
Occupational association to COPD

		Odds Ratio (OR)			
		Crude		Adjusted[a]	
	n	OR	95% CI	OR	95% CI
VGDF exposure					
No exposure	1220	1.00	Reference	1.00	Reference
Any exposure	277	1.69	(0.98-2.91)	**1.98**	**(1.06-3.69)**
Organic dust exposure					
No exposure	1031	1.00	Reference	1.00	Reference
Any exposure	242	1.74	(0.97-3.10)	**2.05**	**(1.04-4.08)**

COPD: Chronic Obstructive Pulmonary Disease. CI: Confidence Interval.
VGDF: Vapour, gas, dust and fume. Bold estimates: Beyond the significance level of 5%.
[a]Random effect logistic regression adjusted for; Pack-year group: <10, 10-20, and >20 smoked pack-years; Age group: 45-54, 55-64, 65-74, 75-84 years of age; General practitioner practice (random variable)

In the mixed model analyses, adjusted for pack-years, age group, and GPP, the adjusted odds ratio (ORadj) in the combined VGDF exposure was significantly associated to COPD; ORadj 1.98 (95% CI: 1.06-3.69). Few women had an occupational exposure to inorganic dust (n=9), fume/gas (n=23), and vapour (n=17), and few exposed cases; 0, 3, and 1, respectively while organic dust exposure was more common and was associated to COPD; ORadj 2.05 (95% CI: 1.04-4.08). The occupational specialists identified 24 women with a tentative farming exposure as 'assisting wife', when excluding this group the association was maintained; ORadj 2.15 (95% CI: 1.06-4.37). Excluding women with prior asthma (n=174) increased both associations of occupational VGDF and organic dust exposure to COPD, ORadj 2.81 (95% CI: 1.36-5.79) and 2.99 (95% CI: 1.37-6.55), respectively. When changing the LLN COPD definition to include mild COPD where women have vague or no symptoms, the associations decreased, but the association to VGDF maintained significance, ORadj 1.74 (95% CI: 1.04-2.91) while the association to organic dust turned into insignificance, ORadj 1.57 (95% CI: 0.89-2.75). The study PAF for COPD was estimated to be 14% in the VGDF exposure and 15% when restricted to the organic dust exposure.

DISCUSSION

The LLN defined age-standardised prevalence of COPD in the population was 4.6%. Occupational VGDF and organic dust exposure was associated to the prevalence of COPD.

COPD

The LLN approach is recommended concurrently by the ERS and ATS [21]. As opposed to the GOLD fixed method which is somewhat biased by participants age, sex and height [27] findings confirmed in the present study with increased prevalence of COPD in the oldest age group calculated by GOLD method compared to the LLN approach. The LLN definition ensures that the participants do have a degree of airflow obstruction outside accepted population norms. However, the 2.5th centile as a diagnostic criterion is a conservative approach, aiming at minimise the percentage of false positives at the expense of an increased number of false negatives.

Furthermore, COPD severity described in the ATS/ERS recommendation utilise the fixed FEV_1 percent predicted [21]. In the present study we have analysed the data based on Quanjer et al. They have recently recommended a new grading of the obstructive lung disease that is clinically relevant and free of biases related to age, height, sex and ethnic group [22]. By adding the restriction of FEV_1 z-score <-2 we obtain a group of subjects having moderate airways obstruction, corresponding the ATS/ERS moderate airways obstruction [22].

Measuring COPD or asthma

The 1993 official statement from ERS [17] and the 2005 ATS/ERS standardisation of lung function testing [21] do not judge a significant positive bronchodilator response to differentiate between asthma and COPD in similar ways. Furthermore, there is no evidence to clearly differentiate asthma and COPD patients by bronchodilator response [21]. The response to bronchodilators varies within and between individuals [28] and when predicted reference values were established as pre bronchodilator values, this lead to some overestimation of the reversibility of a low FEV_1/FVC ratio. In this study asthma was managed in sensitivity analyses by excluding participants with self-reported prior asthma. Asthma predisposes to the development of COPD [29, 30] and may also be associated to the investigated exposures and is therefore a potential confounder. Excluding asthmatics indicated an increased association, but with a wider confidence interval, and the adjusted estimates between exposure and COPD were similar either by including asthma or not.

Occupational exposure assessment

The occupational exposures were assessed by a self-administered questionnaire on exposures and occupation validated with an expert judgment. This approach is considered more sound than questionnaires alone [31], and our results support that the often used self-reported exposures might be prone to bias. This or similar combined approaches is well established and have been utilised in several

population-based retrospective studies [32-34]. Recall bias of occupational exposure might be introduced tending to overestimate the association between exposure and disease, although the risk was considered low, as the questionnaires were filled out before the GP examination, and thus only participants with well known COPD, might have been more aware of job exposures. As patients with mild COPD have vague or no symptoms, this assumption was tested by estimating the association including mild COPD. The estimates were reduced, but the VGDF exposure maintained significant. This result support that our findings only in minor degree are skewed by recall bias, but might lack power. Further, few Danes aged 45 to 84 have knowledge of an association between occupational exposure to VGDF and COPD, and the a priori selected DISCO-88 codes and expert management of each job title into DISCO-88, without awareness of COPD status, have further blinded the exposure assessment.

Smoking assessment

No common conversion of different types of smoking to amount of cigarettes were found (e.g. from the ERS). The utilised equations are clinically used at Aalborg University Hospital, Denmark and nearly the same as Bernaards et al used in a comparison study of calculating pack-years prospectively and retrospectively [35].

Prevalence

The COPD prevalence's estimated in this study, i.e. an age-standardised prevalence of 4.6% are in accordance with other studies from Europe and US where the prevalence in women is reported to be between 4 and 7% using different diagnostic criteria [36-38]. Our study is also in accordance with the review by Halbert et al that estimated a pooled female prevalence from 27 studies to be 5.6% (95% CI: 4.4-7.0) [39]. We have taken a conservative approach with the FEV_1/FVC LLN of 2.5th centile instead of the clinical used 5th centile to reflect a screening setting. This approach gives rise to more false negative and less false positive subjects. Using the clinical FEV_1/FVC<LLN 5th centile (z-score < -1.64) and FEV_1<LLN -2 the age-standardised prevalence was 6% (n=93). As expected the GOLD 2+ prevalence was lower in this study compared to the prior NCPS article where the GOLD 1+ prevalence was estimated (age-standardised 7%) [15] on the same data.

Occupational exposure association to COPD

A novel review by Omland et al [40] identified 29 former population-based studies of occupational exposure to VGDF and COPD, restricting inclusion in their analysis to studies that have used ATS/ERS approved spirometric criteria for defining abnormalities in airflow obstruction and level of FEV_1 [21]. There were differences in associations and exposures in the included studies, but only two with a non significant association both carried out in a younger population [41, 42]. Several

cross-sectional studies have found an association between occupational organic dust exposure in agriculture and COPD [43-45], while the association is less studied solely in women when CODP is based on lung function measurements. Matheson et al estimated a strong association between COPD and organic dust exposure among women, OR 7.43 (95% CI: 2.07-26.7), but this estimate was based on a broader definition of COPD [46]. Studies by Beck et al and Elwood et al estimated a significant decline or lower FEV_1 among female cotton textile workers [47, 48]. The present study found associations within the organic occupational exposure, maybe reflecting the dominating position of agriculture in Northern Denmark as the major occupation for exposure for females to VGDF. We found stronger associations to COPD when excluding subjects with prior self-reported history of asthma. Our estimates are in accordance with the SAPALDIA study where only non-asthmatics of both genders were included. They found an incidence rate ratio of 2.76 (95% CI: 1.32-5.75) for any organic dust exposure in ever smokers and COPD [49]. Although females have been shown to perform work with less respiratory hazards compared to males within the same occupation and industry [50] few studies have analysed for PAF for COPD associated to occupational exposure in females, and none in the same age group as in the present study. Blanc and Torén estimated in their review from 2007 PAF for COPD to be 0 and 1% [11], but these were based on a younger population exposed to dust, and gases and fumes [42]. Our estimates (14% for COPD in exposed to VGDF and 15% in exposed to organic dust) are corresponding well to the 15% PAF for COPD that have been calculated to be aligned in former studies, but based predominately on men [13].

Strengths and limitations

The external study validity is considered to be high in a Western world setting with similar occupational distribution, due to expected similar occupational exposures. The enrolled study population was younger than the non-responders. This might introduce an age dependent healthier study population tending to underestimate the associations. Spirometry error measurements have been managed by regular calibration, but the variations of brands among GPP were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements as recommended by the ERS and the ATS [21]. Possible misclassifications would be of non-differential nature and tend to underestimate the associations. Moreover, when using a spirometrically-defined COPD some COPD patients with compliance difficulties might be excluded from the analysis resulting in false low associations. Information bias of exposure was probably reduced by using the specialist assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. A validation of the self-reported exposures uncovered a large discrepancy between the occupational specialists and the participants regarding relevant exposures due to the stated job titles. This was emphasised by the sub-

analysis where 24 women with a specialist defined tentative exposure, were excluded and slightly increased the association.

CONCLUSION

In this population-based study involving 1626 women we found an age-standardised prevalence of COPD of 4.6%. Organic dust exposure was associated to the prevalence of COPD, independent of smoking habits.

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APPENDIX G. PAPER III

Occupational COPD among Danish never smokers – a population-based study

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Submitted

WHAT THIS PAPER ADDS

- Occupational exposure is an essential risk factor for chronic obstructive pulmonary disease (COPD) among never smokers.
- The method of lower limit of normal (LLN) assessing COPD is recommended by the European Respiratory Society (ERS) and the American Thoracic Society (ATS), but only used in few studies among never smokers.
- In this Danish population-based cohort of 1575 never smokers we estimated a population attributable fraction (PAF) of 48% for occupational exposure to vapour, gas, dust or fumes, which is higher than estimated in earlier studies.
- PAF seems higher when the LLN approach was used compared with the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) approach assessing COPD, although wide and overlapping confidence intervals were given.
- Occupational exposure to vapour, gas, dust and fumes seems to have an even higher impact on COPD among never smokers than previously estimated.

ABSTRACT

Occupational exposures have been shown to be risk factors for chronic obstructive pulmonary disease (COPD) among never smokers. In a Danish population-based cohort we analysed this association and the population attributable fraction. The study population (N=1575) was aged 45-84, COPD was defined by lung function measurements and the method of lower limit of normal (LLN), and the occupational exposure was assessed by questionnaire and expert judgement. Furthermore, the estimates additionally were provided according to the Global Initiative for Chronic Obstructive Lung Diseases (GOLD). More than a threefold increased risk (LLN odds ratio: 3.69 (95% confidence interval (CI) 1.36-10.04) was found for occupational exposure to vapour, gas, dust and fumes (predominantly organic dust) in this never smoking population, with a corresponding 48% (95% CI 30-65) population attributable fraction among never smokers.

INTRODUCTION

Occupational exposures to vapour, gas, dust, and fume (VGDF) have been shown to be risk factors for chronic obstructive pulmonary disease (COPD) among never smokers. Published data suggests a population attributable fraction (PAF) for COPD caused by occupational exposure to be 26-43% among never-smokers.[1,2] We analysed for occupational COPD among never smokers in a Danish population-based study from the cross-sectional North Jutland COPD Prevention Study (NCPS), [3] including an expert assessed job exposure.

METHODS

In 2004-06 the baseline NCPS study recruited by random sampling an age and sex stratified, mixed urban/rural population aged 45-84 from 155 general practitioners (GP). Data consisted of a self-administered questionnaire, pulmonary function tests, height and age. Pulmonary function tests by spirometry (forced expiratory volume per second (FEV_1) and forced vital capacity (FVC)), were performed by the general practitioner or a trained member of the practice staff with the general practitioners own spirometer. Volume and time calibration of the spirometers was performed before study start and every six months by trained staff using a one litre syringe. Adequate spirometry test instructions followed the statement from The European Respiratory Society (ERS) and the standard from The American Thoracic Society (ATS).[4,5] Never smokers accounted for 33% (N=1577) of whom two were excluded due to prior lung cancer. COPD was defined by spirometry according to the method of lower limit of normal (LLN) as pre bronchodilator FEV_1/FVC z-score <2 standard deviations and FEV_1 z-score <2.[6] Data was additionally presented based on the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria with a fixed FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value (GOLD 2+).[7] Both methods of defining COPD reflect moderate airway obstruction and thus comparable severity of obstruction. COPD defined by GOLD was estimated using the post bronchodilator values if pre bronchodilator FEV_1/FVC ratio was <0.70 otherwise the pre bronchodilator values were used. Only participants with FEV_1/FVC ratio <0.70 were projected to perform this reversibility test to minimise costs and time consumption, although post bronchodilator values is recommend by GOLD to exclude reversible obstruction in asthmatics. The Global Lung Function 2012 Equations[8] in the "GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3" was used as the reference population. The occupational exposure assessment was based on a self-administered questionnaire, where the participants were asked for job titles and duration of employment (0, ≤5, 5-9, 10-14, 15-19, and ≥20 years of employment) in jobs with organic dust, inorganic dust, fume/gas, and vapour exposure, respectively. For each exposure category the participants could state their three longest held job titles and appertaining durations. Blinded to COPD status jobs were coded using the Danish version of The International Standard Classification of Occupations

(DISCO-88) [9] and expert derived assessment by two specialists in occupational medicine was used to identify jobs with known exposure to VGDF. Final decision was agreed upon by the two specialists. The total period of employment was calculated by adding the mean years from each five year span of each stated employment. The total duration of employment per exposure was intentionally calculated to define four categories of cumulated duration of exposure: no (0 years), low (<5 years), medium (5-14), and high exposure (≥15 years). However, due to small number of cases and exposed participants at each level we had to dichotomise the exposure category to ever or never. An overall exposure was summarised in a VGDF exposure. Smoking history and prior asthma was obtained by questionnaire.

The McNemar test for matched data was used to compare the two methods of assessing COPD; LLN and GOLD as defined earlier. Data were analysed in a univariate and mixed random effect logistic regression model, with GP practice as random variable, and sex and age as fixed effects. The PAF for COPD was estimated as the proportion of cases exposed*(OR-1)/OR (OR: odds ratio used as proxy for relative risk).[10] Values for the individual PAF equations can be accessed from Table 2 (eg VGDF exposure and LLN: exposed cases/all cases*adjusted OR-1/adjusted OR = (15/15+8)*(3.69-1)/3.69 = 48%). The significance level was set at 5%. The 95% confidence intervals (CI) were calculated using a normal approximation. Statistical analyses were conducted in Stata12.1 (StataCorp LP, 2011). The NCPS-study was performed in accordance to the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

RESULTS

Of 372 DISCO-88 codes 72 were identified with VGDF exposure and occupational exposure were present in 658 (42%) participants in between 1 (72%) and 5 jobs, the most frequent job codes are presented in Table 1.Organic dust exposure was the dominating exposure (86%) while exposure to vapour, gas/fume, and inorganic dust was less common, 5%, 16%, and 21%, respectively. The occupational exposures and the age distribution are presented in the online supplementary Table S1 stratified by sex and combined. There was statistical difference between gender according to age and any occupational exposure, $p<0.001$. COPD defined by LLN was present in 26 participants equal to a prevalence of 1.7%, while the prevalence was 3.4% when COPD was defined by the GOLD criteria (n=53), with a COPD discordance among 31 participants between the two definitions, $p<0.05$. Table 2 show the prevalence's of COPD in the different exposures of VGDF and organic dust, and crude along with adjusted associations between the occupational exposures and COPD. Participants exposed to VGDF and organic dust had an increased prevalence and risk of COPD. Using the GOLD definition of COPD

Table 1: Distribution of the a priori 72 selected Disco-88 codes with known relevant occupational exposure to organic dust, inorganic dust, fume/gas, and or vapour, among *1575* participants[a], and job descriptions of the most frequently applied codes (≥*20* participants).

Job description[b]	DISCO-88	Assigned exposure						
		Organic dust	Inorganic dust	Fume/gas	Vapour	Organic and inorganic dust	Inorganic dust and fume	Inorganic dust, fume and vapour
Field crop and vegetable growers	6111	*21*						
Market-oriented crop and animal producers	6130	*409*						
Bricklayers and stonemasons	7122		*33*					
Carpenters and joiners	7124	*65*						
Varnishers and related painters	7142				*21*			
Welders and flamecutters	7212			*51*				
Sheet-metal workers	7213						*38*	
Cement and other mineral products machine operators	8212		*28*					
Wood-products machine operators	8240	*22*						
Farm-hands and labourers	9211	*61*						
Number of a priori assigned DISCO-88 codes (sum 72)		34	20	3	5	2	7	1
Number of applied DISCO-88 codes among never smokers (sum 40)		19	9	1	4	0	6	1
Number of applied DISCO-88 codes among never smokers with ≥20 participants (sum 10)		5	2	1	1	0	1	0

DISCO-88: Danish adaptation of The International Standard Classification of Occupations (ISCO), revision 1988 (among these ten codes DISCO-88 = ISCO-88).

[a] Missing occupational information in n=*82*

[b] Statistics Denmark (3 April 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx

Italic: No of participants: *20-49,* *50-99* and *>100* (Totally 28% (n=*187*) were assigned to more than one exposure).

Table 2

Prevalence and occupational association of COPD among never smoking Danes, N=1575.

	LLN							GOLD 2+						
	Cases	Total		Crude OR		Adjusted[a] OR		Cases	Total		Crude OR		Adjusted[a] OR	
	n	n	(%)	OR	95% CI	OR	95% CI	N	n	(%)	OR	95% CI	OR	95% CI
VGDF occupational exposure[b]														
No exposure	8	831	1.0	1.00	Reference	1.00	Reference	17	831	2.1	1.00	Reference	1.00	Reference
Any VGDF exposure	15	655	**2.3**	**2.41**	**(1.02-5.72)**	**3.69**	**(1.36-10.04)**	29	655	**4.4**	**2.22**	**(1.21-4.07)**	**3.23**	**(1.55-6.73)**
Organic dust occupational exposure[c]														
No exposure	8	733	1.1	1.00	Reference	1.00	Reference	16	733	2.2	1.00	Reference	1.00	Reference
Any organic exposure	13	562	2.3	2.15	(0.88-5.21)	**2.94**	**(1.05-8.22)**	27	562	**4.8**	**2.26**	**(1.21-4.24)**	**2.79**	**(1.32-5.93)**

CI: Confidence Interval. COPD: Chronic Obstructive Pulmonary Disease. GOLD 2+: Global Initiative for Chronic Obstructive Lung Diseases, defined as fixed forced expiratory volume per second (FEV_1)/forced vital capacity (FVC) ratio<0.70 and FEV_1< 80% of the predicted value. LLN: Lower limit of normal, defined as FEV_1/FVC z-score <2 standard deviations and FEV_1 z-score <2. OR: Odds ratio. VGDF: Vapour, gas, dust and fume.

Bold: Beyond the significance level of 5%.

a Mixed random effect logistic regression model adjusted for; Age group: 45-54, 55-64, 65-74, 75-84 years of age; Sex; General practitioner practice (random variable).

b Missing values: VGDF exposure n=80, spirometry n=7, VGDF and spirometry n=2.

c Missing values: Organic dust exposure n=271, spirometry n=6, organic dust and spirometry n=3.

increased the prevalence and slightly decreased the association with the exposures compared to the LLN definition of COPD. Specific inorganic dust, fume/gas and vapour occupational exposures showed no evidence of an association with COPD (data not shown). Excluding 145 never smokers with prior self-reported asthma (reported as never or ever) in the LLN estimation provided similar associations; VGDF: OR 2.64 (95% CI 0.70-9.92), organic dust: OR 3.43 (95% CI 0.86-13.70). Another important confounder is passive smoking, but only few (n=45) in this population-based study in the age group of 45-84 had never experienced an exposure to passive smoking either at home or at work. Passive smoking was not associated to COPD and additional adjustment for passive smoking changed only to minor extent the estimates. Defined by LLN the study PAF for COPD among never smokers caused by occupational exposure was 48% (95% CI 30-65) for VGDF exposure and 41% (95% CI 19-62) for organic dust exposure only. The corresponding PAF if COPD was defined by GOLD was 44% (95% CI 29-58) and 40% (95% CI 23-57), respectively.

DISCUSSION

In the present study the risk for COPD in never smokers was increased more than three times when occupationally exposed to VGDF and three fold for organic dust despite the low prevalence of COPD (1.7%). However, the calculated associations between occupational exposure and COPD have wide CI due to few cases in each stratum as expected in a population-based setting. Our prevalence estimate was low compared with the prevalence in never smokers from the BOLD Study (0-11%).[11] Here COPD was defined by GOLD criteria stage II or higher in a slightly younger population. When converting our prevalence estimate based on LLN criteria to GOLD criteria the prevalence of COPD increased to 3.4% reducing the difference in the prevalence between the studies. The LLN approach is recommended concurrently by the ERS and ATS [12] as opposed to the GOLD fixed method which is somewhat biased by participants age, sex and height.[13] We have found the highest PAF among studies published in never smokers 48% (95% CI 30-65) [1,2] and higher that the PAF 43% (95% CI 0-68) from the study by Weinmann [14] a study with similar design to the present (defining COPD by LLN and expert assessed occupational exposure). However, a big Chinese population-based study including 6648 never smokers found no significant association between occupational exposure and COPD defined by LLN when using a self-reported occupational exposure assessment among never smokers, OR 1.29 (95% CI 0.92-1.81).[15] This might be a result of non-differential misclassification in the exposure assessment. Recall bias of occupational exposure might be introduced tending to overestimate the association between exposure and disease, although the risk was considered low, as the questionnaires were filled out before the GP examination. We think that only few Danes aged 45 to 84 have knowledge of an association between occupational exposure to VGDF and COPD, and due to the a priori selected DISCO-88 codes and expert management of each job title into

DISCO-88, without awareness of COPD status, the exposure assessment have further reduced the risk of bias. The prevalence of COPD was the same (p=0.13) among participants that have answered questions on work exposure and among those that did not. Information bias of exposure was reduced by using the specialist assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. A validation of the self-reported exposures showed that job titles often were connected to the wrong exposure and the specialists assessed many of the job titles as having no occupational exposure. As a consequence a significant discordance in the four exposure groups was observed comparing the dichotomised expert assessed exposure and the self-reported exposure in the unrestricted data set (N=4717).

The external study validity is considered to be high in a Western world setting with similar occupational distribution and occupational exposures, although the major contribution of organic dust exposure might reflect a special Danish occupational exposure scenario. The enrolled study population included more young women and fewer participants in the oldest group than among non-responders. This might introduce an age dependent healthier study population tending to underestimate the associations. Spirometry error measurements have been managed by regular calibration, but the variations of brands among GP practices were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements as recommended by the ERS and the ATS.[12] Possible misclassification would be of non-differential nature and tend to underestimate the association. Moreover, when using a spirometrically-defined COPD some COPD patients with compliance difficulties might be excluded from the analysis resulting in false low associations.

CONCLUSION

Occupational exposure to VGDF and organic dust significantly increased the risk of COPD corresponding to a high PAF indicating that occupational exposures contributes substantial to the burden of COPD in never smokers. The major contribution of organic dust exposure among the VGDF exposures in this study might reflect a special Danish occupational exposure scenario.

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Online supplementary Table S1: Description of the study population, N=1575.

	Women		Men		Total	
Characteristic	n	(%)	n	(%)	n	(%)
Age						
Age groups						
45 - 54 years	216	(30)	156	(18)	372	(24)
55 - 64 years	193	(27)	190	(22)	383	(24)
65 - 74 years	192	(27)	373	(44)	565	(36)
75 - 84 years	121	(17)	134	(16)	255	(16)
Total	722	(46)	853	(54)	1575	(100)
Mean age (SD)	*62.7*	*(10.8)*	*65.0*	*(9.5)*	*64.0*	*(10.2)*
Occupational exposure						
VGDF duration of occupational exposure (n=1493)						
No exposure	538	(80)	297	(36)	835	(56)
Only low[a] exposures	27	(4)	72	(9)	99	(7)
Medium[b] exposure (and no high)	29	(4)	74	(9)	103	(7)
Any high[c] exposure	80	(12)	376	(46)	456	(31)
Any organic dust (n=1301)	125	(22)	440	(60)	565	(43)
Any inorganic dust (n=1266)	3	(0.5)	137	(21)	140	(11)
Any fume/gas (n=1292)	9	(1)	98	(15)	107	(8)
Any vapour (n=1260)	7	(1)	29	(4)	36	(3)

[a]Low: Exposure but <5 years. [b]Medium: 5 to 14 years of exposure. [c]High: ≥15 years of exposure

VGDF: Vapour, gas, dust and fume. SD: Standard deviation. All variables between sexes, p<0.001.

APPENDIX H. PAPER IV

Occupational exposure increases the four-year incidence of COPD among 45-84-year old Danes

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Submitted

Abstract

The aim was to explore the impact of occupational exposure on the development of chronic obstructive pulmonary disease (COPD) in a longitudinal population-based study among Danes aged 49-89 years.

A stratified sampling was conducted among 155 general practitioners. The four-year follow-up included 1837 males and 914 females corresponding to a follow-up rate of 58%. Information about smoking, occupations and years of occupational exposures were self-reported. Occupations were coded according to the Danish adaptation of The International Standard Classification of Occupations. Exposures to vapour, gas, dust, and fume (VGDF) in each occupation was evaluated by two specialists in occupational medicine. COPD was defined by the 2.5th centile Lower Limit of Normal of FEV_1 and FEV_1/FVC and analysed in a mixed Poisson regression model.

At least one occupation with VGDF exposure was reported by 46%. The adjusted COPD incidence rate ratio (IRR) was associated to occupational exposure especially for low VGDF and organic dust exposure; IRR 3.71 (95% CI: 1.17;11.8) and 3.24 (95% CI 1.07;9.83), respectively, although no clear exposure-response relation was revealed. No significant associations were identified when COPD was defined by the Global Initiative for Chronic Obstructive Lung Diseases.

In summary occupational exposure seems to increase the incidence of COPD.

Introduction

From the age of 30-35 years a decline of lung function occurs as a normal aging process of the lungs [1]. An accelerated decline in lung function over time could be due to environmental exposures and might potentially lead to chronic obstructive pulmonary disease (COPD). Smoking is the major risk factor for COPD, but worldwide, up to half of COPD cases are related to non-smoking causes [2]. Growing evidence suggests that about 15% of COPD could be attributable to occupational exposure [3-5]. Few prospective population-based studies have addressed occupational exposure and COPD incidence and annual change in lung function [6,7]. The aim of the present study was to estimate the contribution of occupational exposure to the incidence of COPD and annual decline in lung function in a population-based study.

Methods

Population

The baseline data was the North Jutland COPD Prevention Study (NCPS) from 2004 [8] and follow-up data was from 2008/2010. The population was selected from two former counties in Denmark (North Jutland and Viborg) with 299,000 inhabitants aged 45-84 years. All Danish citizens have free access to medical care provided by a general practitioner. All 480 general practitioners (GP) in the two counties were invited to participate, Figure 1. The study recruited patients from 155 GP situated in 89 practices (GPP). The Danish individual personal 10-digit Civil Registration System was used to select a randomly, but age (10-year groups) and sex stratified sample of persons aged 45–84 with an overweight of elderly and men, based on the expected Danish prevalence of COPD [9]. The participants consisted of a mixed urban/rural population. In the period October 2004-September 2006, in all 4742 (36%) entered the study, and consulted their general practitioner. Applied baseline data consisted of a self-administered questionnaire, spirometry tests, height and age. Participants with a prior lung cancer were excluded (n=25), leaving 4717 participants at baseline. Follow-up data were assessed between October 2008 and August 2010 and included self-administered questionnaire and spirometry at the GP. The response rate at follow-up was 58%. Seven was excluded due to missing lung function test at baseline and 120 were excluded due to COPD at baseline (LLN defined, see below). The follow-up data consisted finally of 2624 participants.

Spirometry

Pulmonary function tests by spirometry (forced expiratory volume per second (FEV_1) and forced vital capacity (FVC)), were performed by the general practitioner or a trained member of the staff with their own spirometer. Volume and time calibration of the spirometers was performed before study start and every six

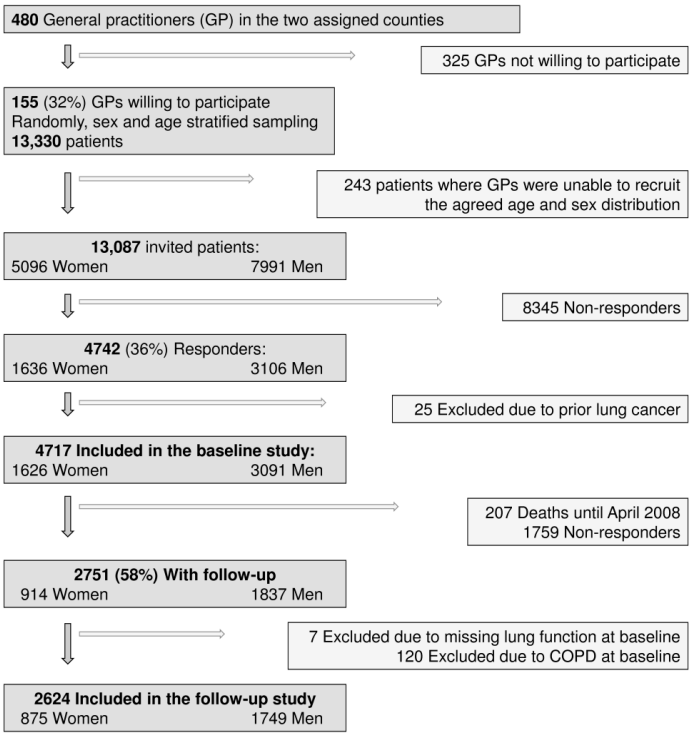

Figure 1 Flow chart of the study enrolment process from baseline (2004) throughout follow-up (2010).

months using a one litre syringe. Adequate spirometry test instructions followed the statement from The European Respiratory Society (ERS) [10] and the standard from The American Thoracic Society (ATS) [11]. For participants with a FEV_1/FVC ratio below 0.70 a reversibility test was performed with eight inhalations of Combivent (1 dose=100 µg salbutamol and 20 µg ipratropium) and spirometry test was assessed after 30 minutes. The reference population used was The Global Lung Function 2012 Equations [12] in the "GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3" and sourced from the Global Lung function Initiative (http://www.lungfunction.org).

COPD and decline in FEV_1 and FVC

We defined COPD by lung function measurements according to the method of Lower Limit of Normal (LLN) for FEV_1/FVC [13]. In a screening setting of normal subjects the LLN is the 2.5th centile (z-score = -1.96) [12]. To distinguish more severe airways obstruction we also added the screening criterion of the LLN for

FEV_1 of a z-score = -2.0 [14]. COPD defined by LLN was estimated using the pre-bronchodilator values. Incidence of COPD was additionally presented based on the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria with a fixed threshold of FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value, GOLD 2+ [15]. COPD defined by GOLD was estimated using the post-bronchodilator values if the pre-bronchodilator FEV_1/FVC ratio was <0.70, otherwise, pre-bronchodilator values were used. When the pre-bronchodilator FEV_1/FVC ratios were <0.70, but no post-bronchodilator values were assessed the pre-bronchodilator values were used. The individual annual change in lung function was calculated as; follow-up data minus baseline data/follow-up time.

Occupational exposure assessment

Occupational exposure was assessed at baseline through a self-administered questionnaire. The participants were asked for duration of exposure (five years span) to organic dust, inorganic dust, fume/gas, and vapour, respectively. For each exposure type the participants could state up to three job titles and appertaining durations (five years span). Jobs where exposure to vapour, gases, dust or fumes (VGDF) were known to be present were selected from the Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) [16] by two specialists in occupational medicine. The final decision on relevant jobs was agreed upon by the two specialists. The exposure assessment was based on the participant listed job titles, and identified job codes. For each of the exposure categories, the total period of employment was calculated by adding the mean years from each five year span of each stated job. The total duration of employment per exposure was then calculated to define four categories of cumulated duration of exposure: no exposure (0 years), low exposure (<5 years), medium exposure (5-14), and high exposure (≥15 years). In one overall VGDF occupational exposure, the "low exposure" was defined to have specific low exposures only, "medium exposure" to have specific medium exposure, but no high exposures, and finally "high exposure" to have any specific high exposure.

Smoking habits

From questionnaires two different smoking variables were estimated never or ever smokers and pack-years. Pack-years were estimated as: ((number of cigarettes smoked per day*number of years smoked)/20). Pack-years were finally reduced to three categories: <10, 10-20, and >20 pack-years, respectively.

Statistics

The annual change (Δ) in FEV_1 and FVC was reported as mean and standard deviations (SD), and analyses of variance were used to compare groups of normally distributed means. Kruskal-Wallis analysis was used for non-normally distributed

data. The chi-square and Fishers exact test for categorical variables was used to assess differences between sub-groups. ΔFEV_1 and ΔFVC were stratified by age (< or ≥60 year at follow-up). The choice of 60 years was applied to identify subjects (<60 years) with ongoing work throughout the study period, reporting no occupational change in-between baseline and follow-up. The COPD incidence was age-standardised to the Danish population. When estimates were based on the GOLD defined COPD, additional 120 participants with baseline GOLD defined COPD were excluded. Mixed Poisson regression model with GPP as random variable was used to estimate the incidence rate ratio (IRR) for COPD and occupational exposures with adjustment for pack-years, sex and age (continuous variable). Additionally the analyses were adjusted for asthma status in-between baseline and follow-up. The McNemar test was used to compare the LLN and GOLD definition of COPD. The combined VGDF occupational exposures were additionally restricted to organic dust, as the main single occupational exposure group. Data didn't reveal the power to analyse the other sub-groups of occupational exposure. The 95% confidence intervals (CI) were calculated using a normal approximation. The significance level was set at 5%. Statistical analyses were conducted in Stata12.1 (StataCorp LP, 2011).

Ethics

The NCPS-study has been performed in accordance to the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

Results

Population

The follow-up population was comparable to the non-participants according to occupational exposure and place of up-bringing (Table 1), while the participants were younger, had better lung function and smoked less. The follow-up age was lower in women compared to men ($p<0.001$). The mean period of follow-up was 3.7 years (SD 0.35; range 2.4-5.0 years). More women than men were never smokers ($p<0.05$), although 16% were current smokers across gender. The population was ethnic homogenous as only eight men (0.3%) were assigned as having 'No Danish descent'. We excluded seven with missing lung function test at baseline, furthermore, 28 lacked spirometry at follow-up. Finally, 2596 had a pre-bronchodilator spirometry, with a subgroup of 433 with a pre-bronchodilator $FEV_1/FVC<0.70$ and 324 performed a reversibility test. When the GOLD and LLN definitions were compared the 109 participants without reversibility test were excluded. Occupational exposure

Table 1:
Description of the baseline charateristics in terms of sex and follow-up participants or non-participants.

	Follow-up participants				Follow-up non-participants			
	Women		Men		Women		Men	
Baseline characteristic	n	(%)	n	(%)	n	(%)	n	(%)
Baseline N=4717	**914**	**(56)**	**1837**	**(59)**	**712**	**(44)**	**1254**	**(41)**
Age groups								
45 - 54 years	**288**	**(32)**	**236**	**(13)**	**221**	**(31)**	**164**	**(13)**
55 - 64 years	**268**	**(30)**	**407**	**(22)**	**152**	**(21)**	**242**	**(19)**
65 - 74 years	**256**	**(28)**	**855**	**(47)**	**170**	**(24)**	**504**	**(40)**
75 - 84 years	**102**	**(11)**	**339**	**(18)**	**169**	**(24)**	**344**	**(27)**
Mean age (SD)	***61.4***	***(10.1)***	***66.5***	***(8.9)***	***63.8***	***(11.6)***	**67.9**	**(9.8)**
Lung function								
FEV_1, L, mean (SD)	***2.35***	***(0.59)***	***3.02***	***(0.81)***	***2.2***	***(0.68)***	***2.78***	***(0.89)***
FVC L, mean (SD)	***3.00***	***(0.71)***	***3.97***	***(0.94)***	***2.87***	***(0.79)***	***3.75***	***(1.00)***
Height cm, mean (SD)	***162.8***	***(6.7)***	*174.9*	*(6.6)*	***163.4***	***(6.4)***	*174.8*	*(6.8)*
Occupational exposure								
VGDF duration of occupational exposure	858	(57)	1774	(60)	647	(43)	1195	(40)
No exposure	702	(82)	670	(38)	524	(81)	434	(36)
Only low* exposures	32	(4)	178	(10)	29	(4)	131	(11)
Medium† exposure (and no high)	33	(4)	226	(13)	30	(5)	134	(11)
Any high‡ exposure	91	(11)	700	(39)	64	(10)	496	(42)
Any organic dust	135	(18)	872	(57)	109	(20)	597	(56)
Any inorganic dust	4	(1)	328	(23)	5	(1)	235	(25)
Any fume/gas	16	(2)	227	(16)	7	(1)	157	(16)
Any vapour	8	(1)	94	(7)	9	(2)	58	(6)
Smoking habits								
Ever-smokers	**482**	**(53)**	**1280**	**(70)**	**409**	**(58)**	**946**	**(76)**
Cumulated smoking								
Mean smoked pack-years (SD)	***15.6***	***(11.3)***	***35.7***	***(28.2)***	***18.1***	***(15.0)***	***38.9***	***(30.6)***
Raised on a farm	379	(42)	875	(48)	287	(41)	549	(44)

FEV_1: Forced expiratory volume per second. FVC: Forced vital capacity. VGDF: Vapour, gas, dust and fume.
SD: Standard deviation. Bold: p<0.05 between participants and non-participants. *Italic: Reported as mean and SD.*
*Low: Exposure but <5 years. †Medium: 5 to 14 years of exposure. ‡High: ≥15 years of exposure.

The specialists considered 72 out of 372 DISCO-88 codes to include relevant exposure to VGDF. Table 2 describes the most frequently used DISCO-88 codes and corresponding distribution of the participant's. There was a substantial gender difference in the assessed DISCO-88 codes as 37% men and 77% women assessed no DISCO-88 code. Assessment of one DICSO-88 code with relevant exposure were seen among 39% men and 15% women, while two-six codes were assessed among 21% men and 2% women. The occupational questions were not addressed among 3% men and 6% women. The dominating occupational exposure was organic dust in men and women, 79% and 86% of the reported exposures, respectively. A considerable number of men were also exposed in the other categories of exposure (Table 1).

Table 2: Distribution of the a priori 72 selected Disco-88 codes with known relevant occupational exposure to organic dust, inorganic dust, fume/gas, and vapour, among *2512* participants*, and job descriptions of the most frequently applied codes (≥*20* participants).

Job description†	DISCO-88	Assigned exposure						
		Organic dust	Inorganic dust	Fume/ gas	Vapour	Organic and inorganic dust	Inorganic dust and fume	Inorganic dust, fume and vapour
Field crop and vegetable growers	6111	*35*						
Dairy and livestock producers	6121	*25*						
Market-oriented crop and animal producers	6130	*660*						
Bricklayers and stonemasons	7122		*63*					
Carpenters and joiners	7124	*124*						
Painters and related workers	7141				*27*			
Varnishers and related painters	7142				*54*			
Welders and flamecutters	7212			*108*				
Sheet-metal workers	7213						*83*	
Metal-heat-treating-plant operators	8123						*23*	
Cement and other mineral products machine operators	8212		*66*					
Wood-products machine operators	8240	*44*						
Grain- and spice-milling-machine operators	8273	*26*						
Farm-hands and labourers	9211	*98*						
Building construction labourers	9313		*60*					
Number of a priori assigned DISCO-88 codes (sum 72)		34	20	3	5	2	7	1
Number of applied DISCO-88 codes in the longitudinal study (sum 48)		24	10	2	5	0	6	1
Number of applied DISCO-88 codes in the longitudinal study with ≥*20* participants (sum 15)		7	3	1	2	0	2	0
Number of applied DISCO-88 codes in the longitudinal study among the women (sum 17)‡		9	3	1	3	0	1	0

DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988

*Missing occupational information, n=*112*

†Statistics Denmark (3 April, 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx

‡All DISCO-88 codes also included men (women range *1-73*), and two codes for organic dust exposure represent ≥*20* participants (6130 and 9211).
Italic; Number of participants: 20-99, 100-199 and 600-699.

Decline in lung function

The overall annual mean (±SD) change in lung function in men was ΔFEV_1 -50 mL/yr (±94) and ΔFVC -58 mL/yr (±133) and in women -31 mL/yr (±69) and -38 mL/yr (±105). The mean annual changes in lung functions stratified by gender and age are presented in the online Supplementary Table S1, adjusted for smoking habits, occupational exposure, asthma in-between baseline and follow-up, whether raised on a farm or not, and combinations of smoking habits and occupational exposure in working participants below 60 years at follow-up. No analyses reach statistical significance. In men (<60 years) with combined exposure from occupation and smoking there was a borderline trend in association in FVC (VGDF; p=0.11, organic dust; p=0.06) and a 2-fold decrease in FVC, and partly in FEV_1 when comparing non-smokers having no occupational exposure, with smokers having an occupational exposure.

Incidence of COPD

During the follow-up period new-onset COPD was identified by spirometry in 1.5% (95% CI: 1.0;1.9) of subjects defined by LLN (n=38) (men 1.7% (95% CI: 1.1;2.4), women 0.9% (95% CI: 0.3;1.6)). The age-standardised estimates were 0.9% (95% CI: 0.9;0.9) (men 1.0% (95% CI: 1.0;1.0), women 0.7% (95% CI: 0.7;0.7)). The GOLD defined COPD incidence was 3.7% (95% CI: 2.9;4.4) (men 4.6% (95% CI: 3.6;5.7), women 1.8% (95% CI: 0.9;2.7)) after additional exclusion of 120 GOLD defined baseline COPD cases, incident cases were n=91. The age-standardised estimates were 2.6% (95% CI: 2.6;2.6) (men 3.0% (95% CI: 3.0;3.1), women 1.6% (95% CI: 1.5;1.6)).

In comparison of the two definitions of COPD there was a significant difference, p<0.01 (also when stratified by sex) with 93 discordant diagnoses between the LLN and GOLD definitions; 6 only had COPD by LLN (men n=3, women n=3) while 87 had COPD by GOLD (men n=73, women n=14).

IRRs from the regression is summarised in Table 3. According to the LLN COPD definition the crude occupational estimates increased after adjustment for pack-years, baseline age, sex and GPP. VGDF exposures and organic dust exposure were associated with COPD, 2-3 folds for VGDF, but with no clear exposure-response relation. No clear association between GOLD defined COPD and occupational exposures were seen. In both definitions of COPD other known risk factors of COPD as smoking and age were associated with COPD as expected. Sub-analyses were performed with adjustment for asthma status between baseline and follow-up. In the LLN analyses this increased the low VGDF association to IRR 4.57 (95% CI: 1.38;15.15) while the high exposure slightly decreased to IRR 2.43 (95% CI: 0.92;6.38), p= 0.07. A similar pattern was revealed for organic dust (low exposure IRR 3.77 (95% CI: 1.21;11.79). Minor changes were seen in the GOLD analyses.

Table 3: Incidence rate ratio of COPD during follow-up due to prior occupational exposure analysed in a Poisson regression, N=2624.

			LLN				GOLD 2+			
			Crude		Adjusted*		Crude		Adjusted*	
	n	(%)	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Regression with VGDF exposure										
Combined VGDF exposure‡										
No	1315	(52)	Ref		Ref		Ref		Ref	
Low	204	(8)	**2.99**	**(1.03;8.67)**	**3.71**	**(1.17;11.8)**	0.98	(0.38;2.50)	0.87	(0.33;2.26)
Medium	240	(10)	1.44	(0.40;5.19)	1.74	(0.44;6.80)	1.42	(0.68;2.98)	0.88	(0.38;2.03)
High	753	(30)	**2.50**	**(1.15;5.44)**	**2.62**	**(1.06;6.48)**	**2.07**	**(1.30;3.29)**	1.44	(0.87;2.39)
Pack-year										
<10	1233	(52)	-	-	Ref		-	-	Ref	
10-20	300	(13)	-	-	**3.54**	**(1.06;11.80)**	-	-	1.74	(0.83;3.68)
>20	834	(35)	-	-	**5.16**	**(1.96;13.59)**	-	-	**2.74**	**(1.63;4.61)**
Sex										
Women	823	(33)	-	-	2.08	(0.78;5.58)	-	-	0.76	(0.39;1.48)
Baseline age			-	-	**1.08**	**(1.03;1.13)**	-	-	**1.06**	**(1.03;1.09)**
Regression with organic dust exposure										
Organic dust exposure†										
No	1220	(56)	Ref		Ref		Ref		Ref	
Low	166	(8)	2.66	(0.95;7.45)	**3.24**	**(1.07;9.83)**	0.81	(0.10;6.48)	0.92	(0.11;7.73)
Medium	204	(9)	1.23	(0.35;4.30)	1.32	(0.35;4.94)	1.25	(0.27;5.84)	1.16	(0.23;5.86)
High	588	(27)	1.91	(0.89;4.11)	2.11	(0.89;5.02)	1.63	(0.60;4.44)	1.59	(0.53;4.81)
Pack-year										
<10	1077	(52)	-	-	Ref		-	-	Ref	
10-20	261	(13)	-	-	**3.54**	**(1.06;11.80)**	-	-	1.81	(0.34;9.54)
>20	725	(35)	-	-	**5.26**	**(2.01;13.74)**	-	-	**3.97**	**(1.26;12.47)**
Sex										
Women	703	(32)	-	-	1.84	(0.71;4.79)	-	-	1.93	(0.59;6.37)
Baseline age			-	-	**1.08**	**(1.03;1.13)**	-	-	**1.07**	**(1.01;1.14)**

CI: Confidence Interval. COPD: Chronic Obstructive Pulmonary Disease. GOLD 2+: Global Initiative for Chronic Obstructive Lung Diseases, defined as fixed forced expiratory volume per second (FEV1)/forced vital capacity (FVC) ratio<0.70 and FEV1< 80% of the predicted value, additional n=120 excluded due to GOLD COPD at baseline. LLN: Lower limit of normal, defined as FEV1/FVC z-score <2 standard deviations and FEV1 z-score <2. Ref: Reference. IRR: Incidence Rate Ratio. VGDF: Vapour, gas, dust and fume.

Bold estimates: Beyond the significance level of 5%.

*Mixed Poisson regression adjusted for; pack-year group, baseline age, sex and general practitioner practice

†Low: Exposure but <5 years, Medium: 5 to 14 years of exposure, High: ≥15 years of exposure. Missing values: Organic dust exposure n=402, Pack-year n=115, organic dust exposure and pack-year n=44.

‡Combined exposure from organic dust, inorganic dust, fume/gas and vapour: Low; Only low exposures, Medium; Medium, but no high exposures, High; Any high exposures. Missing values: VGDF exposure n=112, Pack-year n=145, VGDF exposure and pack-year n=14.

The occupational specialists identified women with a tentative farming exposure as 'assisting wife' (n=13), when excluding this group the associations changed slightly; e.g. low VGDF exposure IRR 3.63 (95% CI: 1.14-11.56).

Discussion

We found a LLN defined age-standardised incidence of COPD of 0.9%. The annual decline in FEV_1 and FVC didn't revealed statistical significance in any of the analysis although in men below 60 years of age the combination of occupational exposure and smoking caused a decline in FVC, with borderline statistical significant trends; VGDF p=0.11 and organic dust p=0.06. However, prior occupational exposures were associated to incident LLN defined COPD by 2-3 folds, but with no clear exposure-response relation.

COPD

ATS and ERS recommend the LLN approach to assess the lung function [13]. This is opposed to the GOLD fixed method which is biased by participant age, sex and height [17]. The LLN definition ensures that the participants do have a degree of airflow obstruction outside accepted population norms. To assess the COPD severity the ATS/ERS recommendation utilise the fixed FEV_1 percent predicted [13]. Nevertheless, we used the LLN approach based on Quanjer et al. clear of biases related to age, height, sex and ethnic group corresponding to the ATS/ERS moderate airways obstruction [14].

Occupational exposure assessment

The occupational exposures were assessed by a self-administered questionnaire on exposures and occupation validated with an expert judgement. This approach is considered more sound than questionnaires alone [18]. Similar combined approaches are well established and have been utilized in several population-based studies [19-21]. Recall bias of occupational exposure was considered low, as the questionnaires were filled out before the GP examination, and only participants with well-known COPD, might have been more aware of job exposures. Furthermore, few Danes have knowledge of an association between occupational exposure and COPD. The a priori selected DISCO-88 codes and expert management of each job title into DISCO-88, without awareness of COPD status, have further blinded the exposure assessment. The approach with four exposure categories is a simplified exposure assessment without consideration of all exposure details. We can´t therefore rule out misclassification of exposure, but if introduced it would be non-differential.

Smoking assessment

We found no common conversion of different types of smoking to the amount of cigarettes. We have applied the equations clinically used at Aalborg University Hospital, Denmark. This was nearly the same equation as Bernaards et al. used in

their comparison study of calculating pack-years prospectively and retrospectively [22].

Annual decline in lung function

The study annual decline in lung function was lower, but with wider variation as compared with the ARIC Study, although our population was older [7]. This might reflect differences in spirometric testing and equipment. However, ethnicity could also play a role. In the study 23% of the participants were black [7], compared to only Caucasians in the present. We found limited non-significant associations between decline in lung function and occupational exposure, only a borderline trend in FVC in men (<60 years) to the combined exposure of occupation and smoking. The short follow-up time and the observed wide range in variation might partly explain our findings.

COPD incidence

The LLN COPD incidence estimated are in accordance with results from the US ARIC Study where the three-year incidence was 2%, though obstruction was defined by LLN 5th centile [7]. We have applied the FEV_1/FVC LLN of 2.5th centile instead of the clinical used 5th centile to reflect a screening setting. This approach gives rise to more false negative and less false positive subjects. The ARIC Study found no association with current or most recent occupation at baseline [7]. In contrast, the SAPALDIA study found dose-dependent associations between VGDF in both LLN and GOLD defined COPD, and only highly exposed LLN were non-significant. The associations ranged from 1.1 to 4.0 [6] similar to the LNN association in the current study. Their occupational exposures were based on current job, duration of current job and a job exposure matrix. We used a cumulative job exposure from all held jobs and extracted the level of exposure based on mean total exposed years in the different jobs. These different approaches might explain the differences in associations. Furthermore, the differences could reflect national variation in the welfare system. In Denmark it might be easier to be retrained, change job conditions or job compared with Switzerland, thus the reason why we find the association more pronounced in the low occupational exposure group might be due to a healthy worker effect. The high effect in the low exposed group could also be a consequence of age differential work procedures. As for instance in farming the younger workers perform the most hard, dirty and dusty tasks, while the elderly will concentrate on less strenuous and cleaner job tasks. The differences between LLN and GOLD might reflect that GOLD defines too many COPD cases alone according to their age, which might dilute the association to the working exposure. Additional adjustment for asthma status between baseline and follow-up increased the IRR among the low occupational exposures using the LLN approach and emphasise the assumed healthy worker effect.

Strengths and limitations

The external study validity is considered to be high in a Western world setting due to similar occupational exposures. The study included more young women and fewer participants in the oldest group than among non-responders. This might introduce an age dependent healthier study population. Spirometry error measurements have been managed by regular calibration, but the variations of brands among GPP were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements [13]. Possible misclassifications would be of non-differential nature and tend to underestimate the associations. Moreover, when using a spirometrically-defined COPD some COPD patients with compliance difficulties might be excluded from the analyses resulting in false low associations. Information bias of exposure was reduced by using the specialist assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. The validation of the self-reported exposures showed that job titles were often stated within the wrong exposure and, furthermore, the specialists assessed many of the job titles as having no occupational exposure.

Conclusion

We have found occupational VGDF and organic dust exposure to increase the incidence of COPD, but without a clear exposure-response relation. However, the study found no statistical significant impact of occupational exposure on the annual declines in FEV_1 and FVC.

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Online supplementary Table S1.
Comparison of annual mean lung function decline* (ΔFEV_1 and ΔFVC) between baseline and follow-up† in women and men, n=2596‡.

	Women					Men				
	n	(%)	Δ FEV_1	p	Δ FVC	p	n	(%)	Δ FEV_1	p	Δ FVC	p
Participants ≥60 years												
Overall	562	(65)	-31.1 ± 76.3		-37.8 ± 109.0		1461	(85)	-51.7 ± 94.1		-59.1 ± 134.5	
Smoking habits												
Never smokers	278	(50)	-27.3 ± 83.1		-33.6 ± 117.1		430	(29)	-49.6 ± 100.6		-56.6 ± 144.6	
Ever smokers	281	(50)	-35.0 ± 69.4	0.23	-41.4 ± 100.8	0.40	1028	(71)	-52.4 ± 91.0	0.62	-59.9 ± 129.6	0.68
< 10 pack-years	371	(71)	-30.0 ± 78.8		-38.5 ± 112.5		568	(41)	-51.1 ± 98.5		-59.9 ± 141.0	
10-20 pack-years	80	(15)	-39.6 ± 55.3	0.20	-46.3 ± 103.1	0.57	165	(12)	-48.4 ± 101.0	0.76	-40.5 ± 140.7	0.12
> 20 pack-years	72	(14)	-29.5 ± 93.0	0.96	-24.8 ± 110.5	0.34	643	(47)	-52.3 ± 88.5	0.82	-60.7 ± 125.8	0.92
Occupational exposure												
VGDF												
Never	412	(80)	-27.7 ± 77.2		-33.3 ± 107.4		531	(38)	-52.8 ± 97.2		-63.6 ± 138.8	
Ever	101	(20)	-41.6 ± 71.0	0.10	-52.4 ± 122.9	0.12	882	(62)	-51.2 ± 93.4	0.75	-57.7 ± 133.0	0.42
Organic dust												
Never	325	(77)	-31.6 ± 69.7		-36.9 ± 103.7		525	(42)	-50.9 ± 96.3		-61.9 ± 137.6	
Ever	96	(23)	-42.9 ± 72.2	0.17	-52.5 ± 126.0	0.27	715	(58)	-51.6 ± 94.4	0.90	-56.4 ± 134.2	0.48
Asthma since baseline												
No	512	(98)	-32.4 ± 65.5		-39.3 ± 102.8		1361	(97)	-50.9 ± 93.6		-58.0 ± 134.6	
Yes	13	(2)	-55.7 ± 153.8	0.60	-30.1 ± 146.5	0.82	42	(3)	-71.7 ± 104.1	0.16	-82.4 ± 136.9	0.25
Raised on a farm												
No	303	(54)	-30.7 ± 68.3		-37.0 ± 103.3		747	(51)	-51.5 ± 93.5		-61.4 ± 133.3	
Yes	257	(46)	-31.6 ± 85.1	0.89	-38.5 ± 115.9	0.87	712	(49)	-51.7 ± 94.9	0.97	-56.4 ± 135.9	0.48

Online supplementary Table S1 (continued).

	Women						Men					
	n	(%)	Δ FEV_1	p	Δ FVC	p	n	(%)	Δ FEV_1	p	Δ FVC	p
Participants <60 years												
Overall	307	(35)	-29.6 ± 53.9		-38.4 ± 96		266	(15)	-40.5 ± 91.1		-52.4 ± 121.4	
Smoking habits												
Never smokers	136	(44)	-32.1 ± 54.8		-44.5 ± 107.4		109	(41)	-38.0 ± 115.3		-37.1 ± 144.4	
Ever smokers	170	(56)	-27.5 ± 53.4	0.47	-33.5 ± 86.1	0.33	157	(59)	-42.3 ± 69.8	0.73	-63.1 ± 101.6	0.11
< 10 pack-years	192	(67)	-28.4 ± 55.1		-37.2 ± 102.5		137	(54)	-38.5 ± 106.7		-43.0 ± 137.5	
10-20 pack-years	40	(14)	-43.0 ± 53.0	0.13	-64.2 ± 81.9	0.12	29	(11)	-17.5 ± 54.2	0.13	-45.0 ± 89.2	0.92
> 20 pack-years	53	(19)	-29.8 ± 52.1	0.86	-29.2 ± 92.2	0.61	89	(35)	-50.9 ± 76.8	0.31	-68.3 ± 107.5	0.12
Occupational exposure												
VGDF												
Never	260	(86)	-30.3 ± 54.5		-40.2 ± 98.7		102	(40)	-34.2 ± 85.3		-44.0 ± 103.0	
Ever	44	(14)	-26.6 ± 52.3	0.67	-31.3 ± 79.3	0.57	152	(60)	-41.4 ± 96.6	0.54	-54.5 ± 129.4	0.47
Organic dust												
Never	248	(90)	-27.5 ± 52.4		-32.5 ± 82.1		110	(51)	-25.8 ± 92.9		-44.4 ± 114.1	
Ever	29	(10)	-23.2 ± 53.3	0.68	-22.4 ± 87.7	0.54	104	(49)	-49.6 ± 99.7	0.07	-59.0 ± 135.9	0.39
Asthma since baseline												
No	288	(98)	-29.2 ± 54.9		-39.1 ± 98.3		261	(98)	-41.5 ± 90.1		-52.5 ± 121.3	
Yes	6	(2)	-21.4 ± 36.9	0.73	-23.7 ± 61.2	0.70	5	(2)	9.7 ± 134.7	0.21	-45.5 ± 144.0	0.90
Raised on a farm												
No	200	(66)	-31.6 ± 55.0		-38.3 ± 90.7		154	(58)	-39.6 ± 81.5		-55.3 ± 109.9	
Yes	105	(34)	-23.9 ± 49.8	0.23	-35.4 ± 103.5	0.80	110	(42)	-42.2 ± 103.8	0.83	-47.8 ± 137.2	0.63
Occupational change inbetween baseline and follow-up												
No	203	(68)	-30.4 ± 54.3		-39.5 ± 88.8		216	(81)	-38.0 ± 81.7		-45.2 ± 114.5	
Yes	95	(32)	-27.7 ± 52.0	0.69	-36.1 ± 111.3	0.80	50	(19)	-51.3 ± 124.3	0.48	-83.4 ± 145.1	0.09

Online supplementary Table S1 (continued).

	Women					Men				
	n	(%)	Δ FEV_1	p	Δ FVC	p	n	(%)	Δ FEV_1	p	Δ FVC	p
Combined smoking and occupational exposure in participants with no occupational change in-between baseline and follow-up												
Never smoked, no VGDF	80	(40)	-35.6 ± 58.5	0.11§	-45.4 ± 95.1	0.09§	43	(21)	-25.6 ± 67.3	0.41§	-26.2 ± 72.9	0.11§
Never smoked, but VGDF	15	(7)	-35.6 ± 50.7	1.00	-60.4 ± 95.2	0.92	44	(22)	-31.3 ± 122.3	0.79	-29.9 ± 163.6	0.89
Ever smoked, no VGDF	92	(46)	-27.6 ± 51.8	0.34	-35.5 ± 85.7	0.48	36	(18)	-33.6 ± 81.3	0.64	-49.2 ± 88.4	0.21
Ever smoked and VGDF	15	(7)	-16.0 ± 52.6	0.23	-9.5 ± 64.1	0.17	81	(40)	-44.0 ± 62.0	0.13	-54.4 ± 101.7	0.08
Never smoked, no organic dust	76	(41)	-31.1 ± 54.6	0.33§	-38.5 ± 87.2	0.18§	41	(25)	-25.1 ± 90.1	0.23§	-34.2 ± 102.0	0.06§
Never smoked, but organic dust	11	(6)	-24.0 ± 43.7	0.68	-46.9 ± 105.0	0.77	34	(20)	-26.2 ± 116.3	0.96	-9.7 ± 156.2	0.43
Ever smoked, no organic dust	90	(48)	-26.5 ± 51.2	0.58	-34.3 ± 79.1	0.74	42	(25)	-24.1 ± 79.4	0.96	-39.3 ± 100.9	0.82
Ever smoked and organic dust	9	(5)	-21.9 ± 63.0	0.64	-1.9 ± 77.9	0.23	49	(30)	-54.7 ± 60.3	0.08	-73.6 ± 103.2	0.07

FEV1: Forced expiratory volume per second. FVC: Forced vital capacity. VGDF: Vapour, gas, dust and fume.
Data are presented as mean ± standard deviation (SD).
*Decline defined as: Follow-up value - baseline value/follow-up time. †Mean follow-up time 3.7 year (sd 0.35): Women: 3.7 yr (0.34); Men: 3.7 yr (0.35).
‡Missing spirometry: Women n=6; Men n=22. §Test of trend across ordered groups.