ARBEJDSBETINGET FALD I LUNGEFUNKTION: ET KENDT PROBLEM MED FORNYET AKTUALITET

Slutrapport til Arbejdsmiljøforskningsfonden

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Indhold

1 Forord

Forskningsprojektet er finansieret af Arbejdsmiljøforskningsfonden (projektnummer: 40-2016-09 20165103813) samt Bispebjerg og Frederiksbergs videnskabelige stipendiepulje. Undersøgelsen blev gennemført som et phd-projekt af læge Stinna Skaaby på Arbejds- og Miljømedicinsk Afdeling, Bispebjerg Hospital. Vejledere for phd-projektet var Jens Peter Bonde, Peter Lange og Esben Meulengracht Flachs. Vivi Schlünssen var external assessor. Phd graden blev opnået d. 27. maj 2021.

Oktober 2021

2 Resumé på dansk

Introduktion: Astma, kronisk obstruktiv lungesygdom (KOL) og kronisk, produktiv hoste er hyppige sygdomme i Danmark. De tre lungesygdomme kan opstå eller forværres af luftbårne stoffer på arbejde, og samlet set vurderes 10–20% af alle tilfælde at skyldes erhvervsmæssig eksponering. Arbejdsmiljøet er dog markant forbedret de seneste årtier med hensyn til luftbåren eksponering. Nyere studier anfægter de påviste sammenhænge mellem arbejde og ovenstående lungesygdomme. Vores formål var at undersøge sammenhængen mellem erhvervsmæssig eksponering og nedsat lungefunktion, kronisk produktiv hoste samt forværring af astma og KOL.

Metoder: Undersøgelsen baserer sig på to befolkningsundersøgelser; Østerbroundersøgelsen og Herlev Østerbroundersøgelsen. Oplysning om jobtitel, rygning, uddannelsesniveau, højde, vægt, spirometri, kronisk produktiv hoste, astma, recepter på perorale kortikosteroider, skadestuebesøg og hospitalsindlæggelser var samlet i registre, spørgeskemaer samt ved klinisk undersøgelse. Vi benyttede jobeksponeringsmatricer til at tildele erhvervsmæssig udsættelse for mineralsk støv, biologisk støv, gasser og dampe, en sammensat variabel bestående af dampe, gasser, støv eller røg (VGDF) samt højmolekylære stoffer, lavmolekylære stoffer og irritanter i hvert job. Sammenhænge blev undersøgt ved brug af mixed effects models, generalized estimating equations og Cox-regression.

Resultater: Erhvervsmæssig eksponering var fra 2003 til 2017 ikke associeret med fald i lungefunktion (FEV1), forværring af astma og KOL eller kronisk, produktiv hoste blandt ikke-rygere. Høje niveauer af alle eksponeringskategorier var associeret med kronisk produktiv hoste blandt rygere med odds-ratioer fra 1,2 (95% konfidensinterval, CI 1,0; 1,4) til 1,5 (95% CI 1,1; 2,0). Fald i FEV1, var i perioden 1976 til 1990 ikke signifikant associeret med dikotomiseret erhvervsmæssig eksponering, mens indekseret eksponering for gasser og dampe var associeret med et fald i FEV1 på 6 ml/ enhed/ år (95% konfidensinterval: 2;11). Kronisk produktiv hoste var i perioden 1976 til 1983 blandt rygere associeret med eksponering for høje niveauer af mineralsk støv, biologisk støv, gasser og dampe og VGDF, og blandt ikke-rygere associeret med høje niveauer af VGDF og lave niveauer af mineralsk støv med odds ratioer mellem 1,3 (95% CI 1,1; 1,6) og 1,7 (95% CI 1,1; 2,4).

Konklusion: Vi fandt ingen signifikant sammenhæng mellem fald i lungefunktion, forværring af astma og KOL samt erhvervsmæssig, luftbåren eksponering fra 2003 til 2017 i to store, danske befolkningsundersøgelser. Kronisk, produktiv hoste var kun signifikant associeret med eksponering på arbejdet blandt rygere i de senere år, mens der sammenhænge blandt ikke-rygere i år før 1990. Udsættelser for gasser og dampe var associeret med fald i lungefunktion før 1990.

Vores resultater viser en sammenhæng mellem fald i lungefunktion og erhvervsmæssige eksponeringer i de tidligere undersøgelser, men ikke i de senere. Der er behov for yderligere undersøgelser, hvor målinger fra arbejdspladser benyttes.

3 Summary in English

Introduction: Asthma, chronic obstructive pulmonary disease (COPD) and chronic productive cough are highly prevalent worldwide. The three lung conditions might be caused or worsened by airborne hazards at work, and an estimated 10–20% are believed to be attributable to occupational inhalant exposures. Airborne occupational exposure levels have, however, generally declined during the past decades, and recent findings question the associations. Our aims were to study the association between past and present occupational airborne exposures and lung function decline, chronic productive cough and exacerbations of asthma and COPD.

Methods: The study was based on two general population-based cohorts; the Copenhagen City Heart Study and the Copenhagen General Population Study. Information on jobs held during follow-up, smoking habits, educational level, height, weight, spirometry, chronic productive cough, self-reported asthma, prescriptions for oral corticosteroids, emergency care unit assessments and hospital admissions were derived from registers, questionnaires, and physical examinations. Occupational exposure to mineral dusts, biological dusts, gases and fumes, a composite variable (vapours, gases, dusts, or fumes; VGDF) as well as high molecular weight sensitizers, low molecular weight sensitizers and irritants were assigned by job exposure matrices. Statistical analyses included mixed effects models, generalized estimating equations and Cox regression.

Results: Selected airborne occupational exposures from 2003 to 2017 were not associated with FEV_1 decline, exacerbations of asthma and COPD or chronic productive cough in non-smokers. High levels of all selected exposures in smokers were associated with chronic productive cough with odds ratios ranging from 1.2 (95% confidence interval, CI 1.0;1.4) to 1.5 (95% CI 1.1;2.0). In analyses including exposures before 1990, dichotomized exposure and FEV_1 decline were not significantly associated. An indexed measure of gases & fumes was associated with an accelerated decline of FEV1 of 6 mL/unit/year (95% confidence interval: 2;11) during 1976–1990. Chronic productive cough was in smokers associated with exposure to high levels of mineral dust, biological dust, gases & fumes and VGDF, and in non-smokers with high levels of VGDF and low levels of mineral dust during 1976–1983, odds ratios ranging from 1.3 (95% CI 1.1;1.6) to 1.7 (95% CI 1.1;2.4).

Conclusion: In our study, occupational airborne exposures were not significantly associated with lung function decline, or exacerbations in asthma and COPD in recent years in two, large Danish cohorts from the general population. Chronic productive cough was associated with selected occupational exposures in smokers only during the time period from 2003–2017, whereas significant associations were seen also in non-smokers in years before 1990. Exposure to gases & fumes was associated with lung function decline in years before 1990. Our results suggest that selected occupational airborne exposures might have accelerated lung function decline decades ago but not in the recent years. Further studies with quantitative exposure assignment and with participants serving as their own controls are warranted.

4 Projektets formål

Undersøgelser inden for forskellige fag og brancher har påvist øget forekomst af kronisk produktiv hoste (vedvarende hoste og opspyt) ved udsættelse for støv. Studier af høj kvalitet, der belyser om lungefunktionen påvirkes, foreligger dog kun i begrænset omfang. Det er usikkert, hvilke typer og niveauer af støvudsættelse, der er skadelige. Spørgsmålet har fået fornyet aktualitet i takt med et markant faldende antal rygere. Tobaksrygning kan tidligere have kamufleret effekten af andre risikofaktorer, som nu får relativt større betydning.

I to store danske befolkningsundersøgelser er der målt lungefunktion, og undersøgelserne er gentaget over mange år. Internationalt er det de hidtil største undersøgelser af arbejdsbetinget tab af lungefunktion målt på antallet af deltagende personer og lungefunktionsmålinger.

Projektets specifikke formål var ud fra disse befolkningsundersøgelser at undersøge sammenhængen mellem erhvervsmæssig, luftbåren udsættelse på danske arbejdspladser og

1. Kronisk, produktiv hoste
2. Accelereret tab af lungefunktion
3. Forværring af astma og KOL

Herunder forskellige *typer* af luftvejseksponering, *intensitet og varighed* samt *tidstrends*.

Projektet skulle kortlægge, hvilke – og hvor mange - erhvervsaktive medarbejdere der er i risiko for at udvikle erhvervsbetinget kroniske obstruktiv lungelidelse (KOL) mhp. at målrette primær og sekundær forebyggelse.

5 Fremgangsmåde

Overordnet studiedesign

Vi undersøgte sammenhængen mellem gennemsnitligt, årligt tab af lungefunktion og erhvervsmæssig luftbåren eksponering. Udsættelsen blev vurderet på basis af en job-eksponeringsmatrice for organisk støv, mineralsk støv og røg/gas med kontrol for en række kendte determinanter for tab af lungefunktion såsom alder, tobaksrygning og social klasse. Undersøgelsespopulationen var Østerbroundersøgelsen og Herlev-Østerbroundersøgelsen, hvor der var foretaget gentagne målinger af lungefunktion med intervaller på omkring 10 år.

Populationer og data

Østerbroundersøgelsen og Herlev-Østerbroundersøgelsen er begge store prospektive befolkningsundersøgelser af indbyggere i København i alderen 20-100 år [1-4]. Ved opfølgningsundersøgelser ca. hvert 10. år blev den oprindelige population geninviteret og samtidig rekrutteret nye deltagere i yngre aldersklasser. Karakteristika er opsummeret i tabel nedenfor.

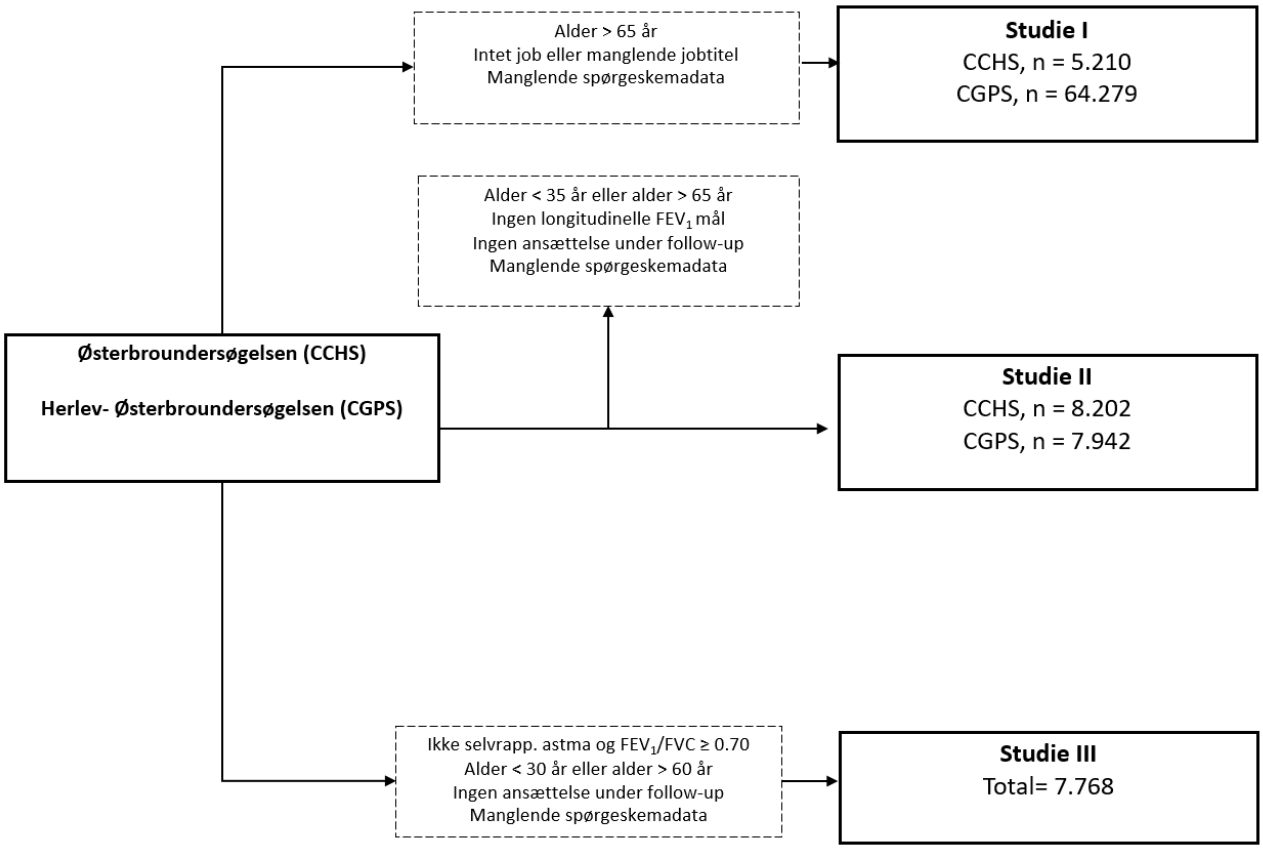
	Østerbroundersøgelsen	**Herlev-Østerbroundersøgelsen**
Antal deltagere (1. runde)	14.223	110.000
Design	Prospektiv kohorte	Prospektiv kohorte
Årstal	1976-2015	2003-2016
Follow up*, år	35	10
Lungefunktionsmåling, antal	5	2
Reversibilitetstest**	Ja, en subpopulation	Alle deltagere i 2. runde
*Follow up er angivet frem til dags dato. Reversibilitetstest: ** Reversibilitetstest udført, hvis lungespirometri har vist obstruktiv lungefunktionsnedsættelse.		

Tabel 1. Studiepopulationer

For begge befolkningsundersøgelser forelå spørgeskemadata om køn, alder, socioøkonomisk position, jobtitel i 1. -3. runde af Østerbroundersøgelsen, helbredsforhold og kroniske sygdomme samt

om risikofaktorer for blandt andet kronisk obstruktiv lungesygdom. Der var detaljeret information om tidligere og aktuel tobaksrygning, passiv rygning, body mass index, astma i familien samt luftvejsproblemer i barndommen. Spirometrisk lungefunktionsmåling var udført ved alle undersøgelser i begge kohorter.

Vi gennemførte tre studier med in- og eksklusionskriterier som beskrevet i figur nedenfor.



Figur 1. In- og eksklusionskriterier til tre studier i projektet.

Eksponering

Erhvervsmæssig udsættelse for partikler blev karakteriseret ved en kombination af tidligere metoder. Vi belyste tre faktorer: Type af eksponering, varighed og intensitet.

Type af eksponering: Følgende overordnede kategorier blev valgt: Organisk støv, mineralsk støv, gasser og røg samt højmolekylære stoffer, lavmolekylære stoffer og irritanter. Eksponeringen blev

estimeret på baggrund af en række trin. Jobtitler for alle deltagere blev indhentet ved kobling til DOC*X databasen i Danmarks Statistik. Her var jobtitler og erhvervstilknytning for alle danskere fra 1970 og 1976 og frem til i dag oparbejdet, dokumenteret og valideret [5]. Disse jobtitler var kodet efter DISCO-88 fagklassifikationen. DISCO er den danske version af den internationale fagklassifikation, International Standard Classification of Occupations (ISCO).

På basis af DISCO-88 koder for jobtitel blev eksponering klassificeret ved hjælp af to jobeksponeringsmatricer (JEM). Matricerne bestod af to dimensioner - stillingstype på den ene akse og eksponering på den anden akse. Vi anvendte to ekspertvurderede jobeksponeringsmatricer: Airborne Chemical Job Exposure Matrix (ACEJEM) [6] og Occupational Asthma-specific JEM (OAsJEM) [7]. Inddelingen var baseret på prævalens og intensitet af eksponering i hver stillingstype. Begge jobeksponeringsmatricer var tidligere benyttet i lignende studier.

Varighed af eksponeringen blev estimeret på baggrund af kalenderårsspecifikke data om hver deltagers arbejdsliv fra DOC*X databasen. Herved kunne antallet af år med eksponering for partikler i en given followup-periode bestemmes.

Intensiteten af den arbejdsmæssige udsættelse for partikler blev angivet på baggrund af jobeksponeringsmatricer for hver stillingstype. Herved kunne eksponeringen tillægges en ekstra dimension.

Udfald

Undersøgelsens udfald var i det ene studie baseret på spørgeskemadata. Her havde man spurgt deltagerne: ”Hoster du slim op (om morgenen eller i løbet af dagen) i op til tre måneder hvert år?”
I det andet studie var udfaldet beregnet ud fra spirometri foretaget ved klinisk undersøgelse, mens studie 3 var registerbaseret ved indløste recepter på orale kortikosteroider, skadestuebesøg eller indlæggelser relateret til astma eller KOL under opfølgningsperioden (se nedenfor).

Udfald	Type of data	Beskrivelse
Kronisk produktiv hoste	Spørgeskema	*Hoster du slim op (om morgenen eller i løbet af dagen) i op til tre måneder hvert år?*
Ændring i lungefunktion	Klinisk undersøgelse	Gennemsnitlig årlig ændring i FEV_1 beregnet på baggrund af spirometri fra to forskellige undersøgelsesrunder
Eksacerbation	Registerbaseret	Recepter på orale kortikosteroider, skadestuebesøg eller indlæggelser relateret til astma eller KOL under opfølgningsperioden

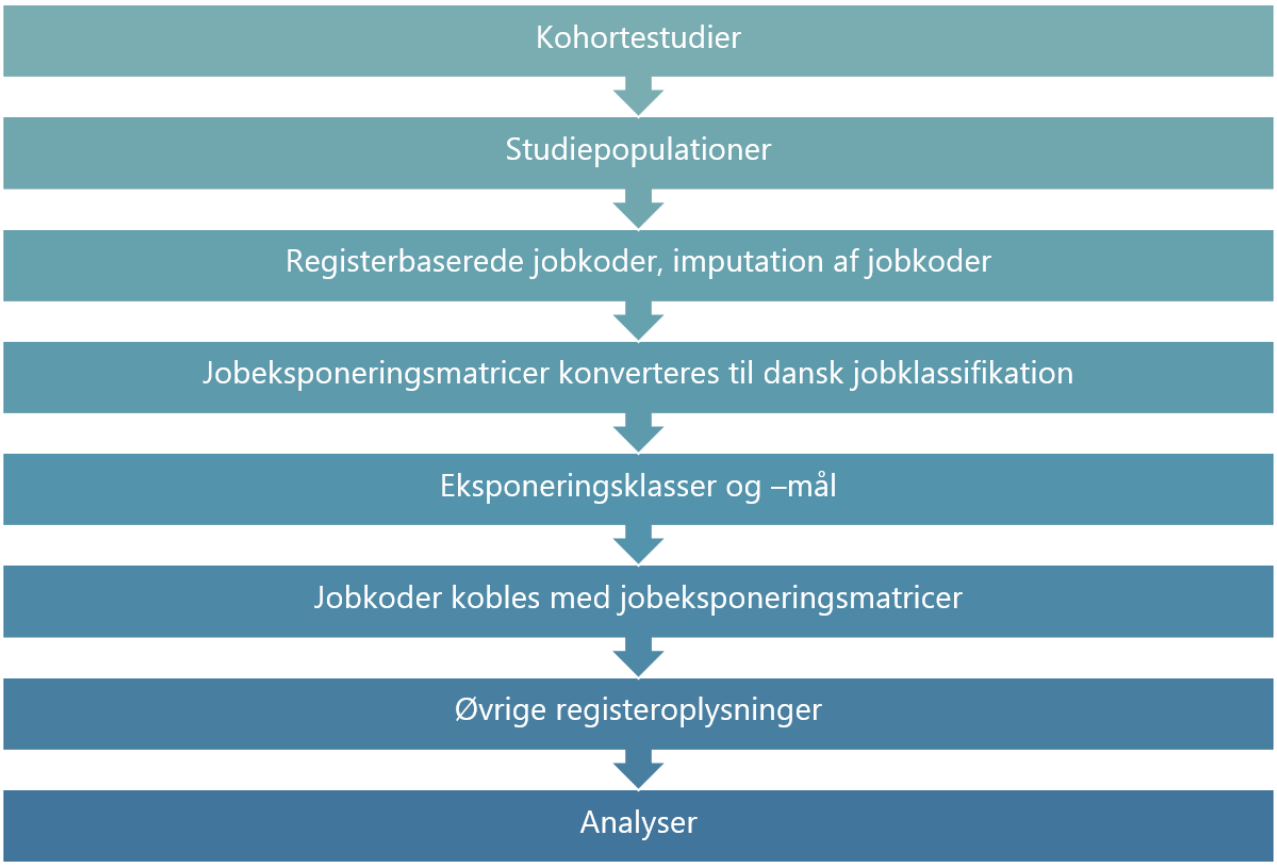
Tabel 2. Oversigt over udfald

Statistisk analyse

Vi anvendte generalized estimating equations (GEE) til analyser af gentagne, binære udfald. Til analyser med gentagne, kontinuerte udfald brugte vi mixed effects models med ustruktureret kovarians. Til at belyse associationer mellem eksponering og eksacerbationer i astma og KOL brugte vi Multivariat Cox regression med alder som underliggende tidsskala og tidsvarierende eksponering.

Udførelse

Nedenfor ses oversigt over vigtige trin i projektet.



Figur 2. Overordnede trin i projektet.

Tidsforløbet er beskrevet i tabel 3.

Marts 2018 -	Indskrivning på ph.d.-skolen Validering af jobeksponeringsmatrice Data om patientens erhverv fra Østerbrundersøgelsen samkøres med DOC*X-projektet (Danish Occupational Cohort)
2019	Datatræk og datamanagement
2019	Data fra Østerbrundersøgelsen analyseres ud fra Danmarks Statistisk
2019	Data fra Herlev- Østerbrundersøgelsen analyseres ud fra Danmarks Statistisk
2020 – marts 2021	Sammenskrivning af artikler og udformning af ph.d.

Tabel 3. Tidsforløb.

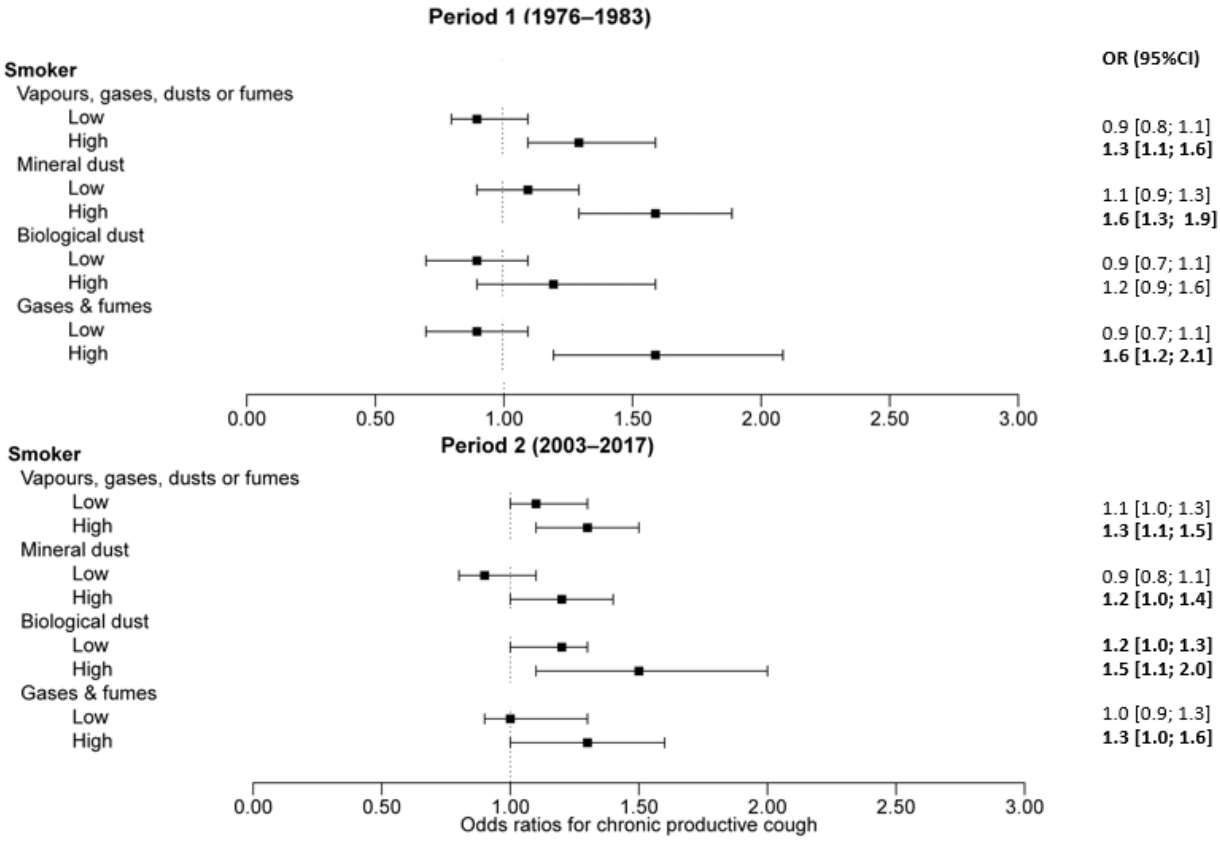
Studiet blev udført på Arbejds- og Miljømedicinsk Afdeling på Bispebjerg Hospital under vejledning af professor i arbejdsmedicin, Jens Peter Bonde. Den ph.d.-studerende, læge Stinna Skaaby, var indskrevet ved Public Health and Epidemiology, ph.d.-skolen, Københavns Universitet.

6 Hovedresultater

Kronisk produktiv hoste

Vi opdelte alle analyser på periode og rygestatus. Blandt ikke-rygere justerede vi for om deltagerne var aldrig-rygere og tidligere rygere, og blandt rygere for hvor meget de røg. Analyserne blev desuden justeret for alder over og under 50, køn, BMI og uddannelse.
Nedenfor er hovedresultater præsenteret for hhv. rygere og ikke-rygere samt tidsmæssigt opdelt.

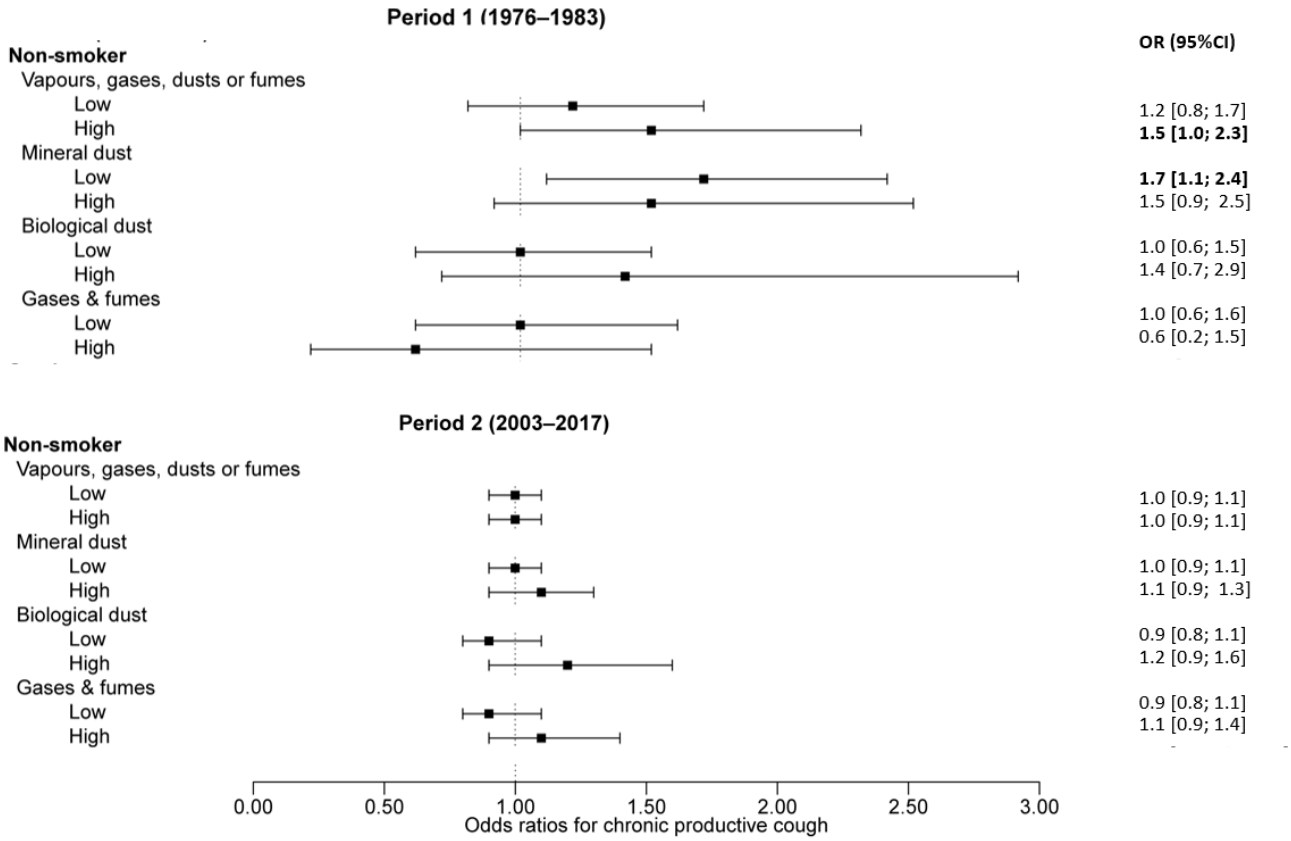
Rygere



Tabel 4. Kronisk produktiv hoste blandt rygere og arbejdsmæssig eksponering

Hvis man ser på det samlede eksponeringsmål VGDF for rygere i den tidlige periode, var høj eksponering sammenlignet med ingen eksponering signifikant associeret med kronisk produktiv hoste med en odds ratio på 1.3. Lignende associationer så vi i undergrupperne af høj eksponering for mineralsk støv og gasser & røg, mens høj biologisk støveksponering kun var grænsesignifikant. Vi genfandt associationerne i den sene perio-

de, hvor både eksponering for lavt og højt biologisk støv sammenlignet med ingen eksponering var signifikant associeret med kronisk produktiv hoste.

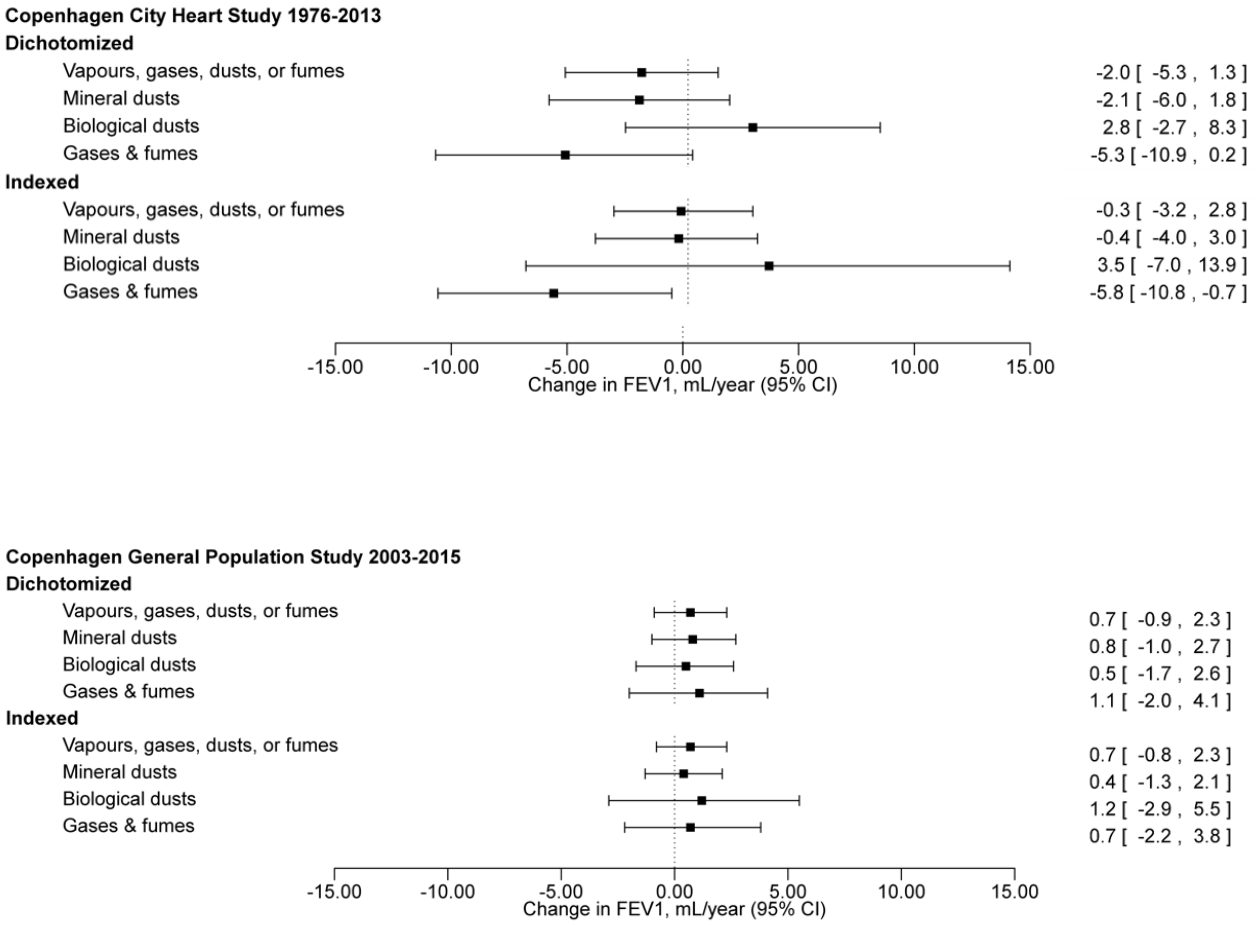


Tabel 5. Kronisk produktiv hoste blandt ikke-rygere og arbejdsmæssig eksponering

Blandt ikke-rygerne så vi tendens til lignende sammenhænge, men kun signifikante associationer for høj VGDF eksponering og lav mineralsk støv. Vi så ingen associationer blandt ikke-rygere i den sene periode

Ændring i lungefunktion

I studiet vedrørende ændring i lungefunktion opdelte vi alle analyser på kohorte og justerede for køn, højde, vægt, gennemsnitlig pakkeår per år, uddannelse og baseline FEV_1.



Tabel 6. Ændring i lungefunktion (FEV_1) og arbejdsmæssig eksponering

I Østerbroundersøgelsen var eksponering for gasser og røg sammenlignet med ingen eksponering for gasser og røg associeret med et årligt fald i FEV_1 på 6 mL. Sensitivitetsanalyser viste, at associationen kun sås i de tidlige år fra 1976-83.

I Herlev- Østerbroundersøgelsen fandt vi ingen signifikante sammenhænge mellem eksponering og ændring i lungefunktion.

Forværring af astma og KOL

Alle analyser i studiet af forværring af astma og KOL var justeret for køn, BMI, uddannelse, rygning, FEV_1 % prædikteret klasse og forværring året før baseline. Vi fandt ingen signifikante associationer mellem de udvalgte eksponeringer og eksacerbationer af KOL og astma.

7 Diskussion

Det er vanskeligt at finde studier, der er sammenlignelige med vores resultater på meget detaljeret niveau. En meta-analyse af kronisk bronkitis og arbejdsmæssige eksponering tildelt ved jobeksponeringsmatricer med eksponeringstid fra 1960 til 2010 fandt odds ratioer, der var i tråd med vores fund for rygere [8]. Meta-analysen justerede for, men stratificerede ikke på rygning.

Vi fandt ingen sammenhæng mellem udsættelse for mineralsk støv, biologisk støv eller VGDF og ændring i lungefunktion målt ved FEV_1. Der findes kun få longitudinelle befolkningsundersøgelser, hvor sammenhængen mellem arbejdsmæssig eksponering og ændring i lungefunktion er undersøgt. [9-17]. Fundene har været inkonsistente. Der findes ikke meta-analyser af overordnet eksponering for mineralsk støv eller gasser og røg og ændring i lungefunktion i industrispecifikke studier. I en metaanalyse af organisk støveksponering i industrispecifikke, longitudinelle studier fandt man et samlet ekstra fald i FEV_1 på 5 mL pr år blandt eksponerede sammenlignet med kontroller [18]. Fundene var dog inkonstistente, og man konkluderede, at der kun var begrænsede holdepunkter for en kausal sammenhæng mellem eksponering og ændring i lungefunktion.

Der findes ikke tidligere undersøgelser til sammenligning, der har set på erhvervsmæssig eksponering og forværring af både astma og KOL.

8 Konklusioner og perspektiver

KOL har store konsekvenser for den enkelte og for samfundet. Studiet har bidraget til at belyse sammenhænge mellem erhvervsmæssig eksponering og udvalgte lungesygdomme. Resultaterne forventes at have interesse samfundsmæssigt og for arbejdstagere, arbejdsgivere, Arbejdstilsynet, andre offentlige myndigheder som Arbejdsmarkedets Erhvervssikring samt internationale selskaber. Projektet er det første på området med et så stort antal deltagere i en befolkningsundersøgelse, så lang follow up-tid og så detaljeret information om jobtitel - og dermed eksponering. Derfor vil resultaterne have større gennemslagskraft end mindre studier og dermed et større forebyggelsespotentiale.

Vi planlægger et studie af sent debuterende astma med brug af samme jobeksponeringsmatricer. I fremtidige studier bør jobeksponeringsmatricer generelt forfines gerne med målinger foretaget på arbejdspladser. Metoden bør gentages, hvor større, skandinaviske befolkningsundersøgelser kombineres, og landbefolkningen også inddrages for at opnå større eksponeringskontrast og mere styrke. Der er igangværende studier, som ser på lungeudvikling igennem hele livet, herunder også gen-miljøinteraktion. Det åbner mulighed for bedre at kunne identificere personer, der dårligt tåler inhalérbare stoffer.

9 Formidling

Projektets hensigt og formål er opnået gennem:

- Udarbejdelse og publikation af tre artikler i peer reviewede tidsskrifter
- Udarbejdelse af afhandling
- Det samlede arbejde præsenteret og forsvaret ved et phd forsvar
- Udarbejdelse af lægmandsartikel
- Præsentation af resultater på nationale og internationale faglige konferencer
- Præsentation for interne og eksterne samarbejdspartnere
- Præsentation af resultater for brancheklub

Grundet covid-restriktioner er videreformidling af studiernes resultater til lægmand og på internationale konferencer først lige begyndt.

9.1 Fortegnelse over publikationer og produkter fra projektet

Chronic productive cough and inhalant occupational exposure – a study of the general population. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Nordestgaard BG, Sadhra S, Kurmi O and Bonde JPE. International Archives of Occupational and Environmental Health, 2021, 1-8.

Occupational inhalant exposures and longitudinal lung function decline. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Çolak Y, Afzal S, Nordestgaard BG, Sadhra S, Kurmi O and Bonde JPE. Online 2021 May 6; Online ahead of print., European Respiratory Journal.

Occupational exposures and exacerbations of asthma and COPD-A general population study. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Nordestgaard BG, Sadhra S, Kurmi O, Bonde JPE. Plos one, 2020, 15.12: e0243826.

Occupational exposure and chronic airway disease, PhD Thesis. Stinna Skaaby.

Dansksproget artikel: Lunger på arbejde. Stinna Skaaby 2021.

Lung function decline and occupational exposures. Posterpræsentation. Årsmøde, Arbejds- og Miljømedicinsk Selskab, 2016

Indlæg på Arbejds- og Miljømedicinsk Afdelings LinkedIn.

9.2 Mundtlig formidling

Occupational exposure and chronic airway disease. Phd forsvar, maj 2021

Oral presentation, 28th International Symposium on Epidemiology in Occupational Health
From the Workplace to the Population: Exposure and Prevention October 25-28, 2021

Kroniske lungesygdomme og arbejde. Uddannelseskonference Bispebjerg Hospital 2021

Tab af lungefunktion – et arbejdsmæssigt problem? Forskerforum Bispebjerg Hospital 2020 og 2021

Oplæg om lungesygdom og arbejdsmiljø på baggrund af projektets resultater, Snedker-Tømrernes Brancheklub i København, september 2021

Oral presentation, Open DOC*X- Research Seminar, The National Research Center for the Working Environment, 2018

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Lunger på arbejde

Af Stinna Skaaby

WHO har i 2007 anbefalet, at arbejdsrelaterede kroniske lungesygdomme identificeres, diagnosticeres og forebygges bedre. På arbejde kan man ved indånding af luft udsættes for stoffer, hvoraf nogle er mistænkt for at øge risikoen for lungesygdom. Kronisk produktiv hoste med opspyt af slim, kronisk obstruktiv lungesygdom (KOL) og forværring af eksisterende lungesygdom forekommer hyppigt. Nogle tilfælde mener man skyldes eksponeringer på arbejdet. Mange rammes af alle tre lidelser, og globalt anslås det, at 250 millioner mennesker lider af kronisk obstruktiv lungesygdom.

Tabel 1. Faktaboks. Tre hyppige lungelidelser	
Kronisk hoste med opspyt af slim	Hoste med opspyt minimum 3 måneder hvert år
Kronisk obstruktiv lungesygdom (KOL)	Kronisk lungesygdom med forsnævrede luftveje og destruktion af lungevæv
Forværring af astma og KOL	Forværring udover dag-til-dag variation, der kan kræve indlæggelse

På arbejdspladser kan man udsættes for påvirkning ved indånding af luft. Nogle kan ses, andre kan lugtes, atter andre kan ikke registreres. Man inddeler ofte luftbåren eksponering i gasformer og aerosoler (tabel 2).

Tabel 2. Inddeling af luftbåren eksponering
Gasformer: Gas og damp (væske eller stof i gasform)
Aerosoler: Flydende stof eller faste partikler i luften (støv og røg)

Oftest udsættes man for flere stoffer på samme tid, f.eks vil en svejser være udsat for både gas, røg og støv, og en maler for damp og støv. Det, der sker med aerosoler og gasser i lungerne, afhænger af adskillige faktorer. Én faktor er størrelsen af partikler. Næse og svælg fungerer som et filter, hvor større partikler fanges. Mindre partikler kan bevæge sig længere ned i luftvejene. Raske lunger beskyttes blandt andet af små fimrehår, et tyndt lag slim og hosterefleksen mod partikler. Slim kan hostes op af de større luftveje, men ikke fra de mindste luftveje. Ved kronisk produktiv hoste ophobes slimen, og inflammatoriske celler kommer til. KOL karakteriseres ved forsnævrede luftveje, og i lungerne ses varierende grader af forandringer. Destruktion af de yderste lungeafsnit, alveolerne, kaldes emfysem og forekommer ofte, men ikke altid. Symptomerne på KOL er åndenød, hoste og opspyt af slim. Mange, men ikke alle KOL-patienter vil opleve perioder med kronisk produktiv hoste.

Graden af forsnævrede luftveje måles ved hjælp af lungefunktionsundersøgelse. Lungefunktionen stiger fra barndommen til 20-års alderen. Efter en varierende plateaufase i starten af 30'erne, falder lungefunktionen gradvist med alderen. KOL blev indtil for få siden opfattet som et resultat af mange års for kraftigt fald i lungefunktion. Fald i lungefunktion afhænger dog også af den maksimalt opnåede lungefunktion. Man ved nu, at lungeudvikling både inden fødslen og i barndommen spiller en rolle for maksimalt opnået lungefunktion og formentlig også for det efterfølgende fald.

De største risikofaktorer for kronisk sygdom i luftvejene er rygning, både passiv og aktiv, indendørs og udendørs luftforurening, allergifremkaldende stoffer, arbejdseksposition, alder og genetik. Langt de fleste af disse kan forebygges.

Man har i tidligere, større undersøgelser fundet stærke holdepunkter for en sammenhæng mellem arbejdsmæssig eksponering og KOL både inden for samme og på tværs af industrier. Der er dog de seneste årtier sket et markant fald i arbejdsmæssig luftbåren eksponering, og det er usikkert, om der fortsat er en sammenhæng.

Studiemetode

Vi anvendte data fra udvalgte deltagere i to store, danske befolkningsundersøgelser: Østerbroundersøgelsen blev initieret i 1976, og 5. runde blev afsluttet i 2015. Herlev-Østerbroundersøgelsen var den anden befolkningsundersøgelse, hvor 2. runde fortsat er i gang. Deltagerne var tilfældigt udvalgt til første runde af begge befolkningsundersøgelser.

Deltagerne fik ved hver undersøgelse udleveret et spørgeskema og fik foretaget en klinisk undersøgelse, herunder lungefunktionsundersøgelse (spirometri). Vi undersøgte deltagere mellem 30-35 år og op til 65 år. For alle deltagere hentede vi årlige joboplysninger via DOC*X, som er et dansk register med oplysninger om danskeres erhvervshistorik tilbage fra 1970. Hver jobtitel blev herefter koblet med en jobeksponeringsmatrice for at tildele arbejdsmæssig eksponering. Alle analyser blev opdelt efter periode og rygestatus. Analyserne blev desuden justeret for alder, køn, BMI og uddannelse.

Resultater

Der var en sammenhæng blandt rygere mellem høj udsættelse for enten gas, damp, røg eller støv og kronisk produktiv hoste. Blandt ikke-rygere var der i de tidlige undersøgelser en sammenhæng mellem kronisk produktiv hoste og høj udsættelse for enten gas, damp, røg eller støv, mens der i nyere år ikke fandtes en sammenhæng.

I de tidlige undersøgelser fra 1976 – 1983 var udsættelse for gasser og røg på arbejdet associeret med et årligt fald i lungefunktion (FEV_1) på 6 mL. Vi fandt ingen sammenhænge i de senere undersøgelser.

Vi fandt ingen sammenhænge mellem de udvalgte eksponeringer og forværring af KOL og astma.

Diskussion

Vores resultater tyder på, at eksponering for luftbårne stoffer på arbejdet kan have bidraget til udvikling af KOL for flere årtier siden. I nyere undersøgelser så vi kun sammenhænge mellem kronisk produktiv hoste og arbejdsmæssig eksponering blandt rygere. Man kan derfor med fordel rette forebyggelse mod denne gruppe.

Slutregnskab

Projekt nr. 40-2016-09 20165103813

Projekttitel **Arbejdsbetinget tab af lungefunktion. Et kendt problem med fornyet aktualitet**

UDGIFTER	Regnskab 2017	Regnskab 2018	Regnskab 2019	Regnskab 2020	Regnskab 2021	Total	Godkendt budget
LØNUDGIFTER							
VIP							
VIP/AC	kr -	kr 467.881	kr 553.094	kr 524.490	kr -	kr 1.545.466	kr 1.215.000
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
I alt VIP	**kr -**	**kr 467.881**	**kr 553.094**	**kr 524.490**	**kr -**	**kr 1.545.466**	**kr 1.215.000**
TAP							
TAP	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
I alt TAP	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**
Andet							
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
I alt Andet	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**
DRIFTSUDGIFTER							
Driftsudgifter	kr -	kr -	kr -	kr -	kr -	kr -	kr -
Materialer	kr -	kr -	kr -	kr -	kr -	kr -	kr 15.000
Formidling	kr -	kr 187	kr -	kr 10.392	kr -	kr 10.579	kr 25.000
Rejseomkostninger	kr -	kr -	kr 2.466	kr -	kr -	kr 2.466	kr 65.000
Registerbehandling	kr -	kr 3.450	kr 9.012	kr 13.690	kr -	kr 26.152	kr 30.000
Studieafgift KBH	kr -	kr 50.000	kr 50.000	kr 50.000	kr -	kr 150.000	kr 150.000
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
I alt	**kr -**	**kr 53.637**	**kr 61.478**	**kr 74.082**	**kr -**	**kr 189.197**	**kr 285.000**
20% overhead	**kr -**	**kr 104.304**	**kr 122.915**	**kr 119.714**	**kr -**	**kr 346.933**	**kr 300.000**
Udgifter u. overhead							
Ekstern tjenesteydelse	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
	kr -	kr -	kr -	kr -	kr -	kr -	kr -
I alt	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**	**kr -**
TOTAL	**kr -**	**kr 625.822**	**kr 737.487**	**kr 718.286**	**kr -**	**kr 2.081.595**	**kr 1.800.000**

NB: Institutionens projekansvarlige skal underskrive slutregnskabet:

Dato: 13/4-2021

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ORIGINAL ARTICLE

Chronic productive cough and inhalant occupational exposure–a study of the general population

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Abstract

Purpose Occupational inhalant exposures have been linked with a higher occurrence of chronic productive cough, but recent studies question the association.

Methods We included participants from two general population studies, the Copenhagen City General Population Study and the Copenhagen City Heart Study, to assess contemporary (year 2003–2017) and historical (1976–1983) occupational inhalant hazards. Job titles one year prior to study inclusion and an airborne chemical job-exposure matrix (ACE JEM) were used to estimate occupational exposure. The association between occupational exposures and self-reported chronic productive cough was studied using generalized estimating equations stratified by smoking status and cohort.

Results The population consisted of 5210 working individuals aged 20–65 from 1976 to 1983 and 64,279 from 2003 to 2017. In smokers, exposure to high levels of mineral dust, biological dust, gases & fumes and the composite variable vapours, gases, dusts or fumes (VGDF) were associated with chronic productive cough in both cohorts with odds ratios in the range of 1.2 (95% confidence interval, 1.0;1.4) to 1.6 (1.2;2.1). High levels of biological dust were only associated with an increased risk of a chronic productive cough in the 2003–2017 cohort (OR 1.5 (1.1;2.0)). In non-smokers, high levels of VGDF (OR 1.5 (1.0;2.3)) and low levels of mineral dust (OR 1.7 (1.1;2.4)) were associated with chronic productive cough in the 1976–1983 cohort, while no associations were seen in non-smokers in the 2003–2017 cohort.

Conclusion Occupational inhalant exposure remains associated with a modestly increased risk of a chronic productive cough in smokers, despite declining exposure levels during the past four decades.

Keywords Occupation · Work · Chronic cough · Chronic bronchitis

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Introduction

Chronic productive cough (chronic bronchitis) is traditionally defined as cough and sputum expectoration for at least three months in two consecutive years (Irwin et al. 2006) and is a validated measure in respiratory epidemiology (Fletcher et al. 1974). It is prevalent in the general population (Cerveri et al. 2001; de Oca et al. 2012; Ferre et al. 2012) and associated with acute respiratory exacerbations, an excess loss of lung function and marginally higher mortality (Lange et al. 1990b; Vestbo et al. 1996). The main risk factor for chronic productive cough is tobacco smoking, and other causes include gastroesophageal reflux, rhinosinus disease and occupational inhalant hazards. Occupational inhalant exposures are often divided into subgroups such as vapours, gases, dusts (mineral and biological) and fumes, or expressed as a combined measure of all these.

In 2019, the estimated occupational attributable fraction for chronic productive cough was 13% (Blanc et al. 2019). Occupationally exposed workers are not routinely screened for chronic productive cough but general practitioners are advised to question patients with a chronic productive cough about inhalant hazards in the workplace (Irwin et al. 2006). Health records on chronic cough and occupational hazards from general practitioners are often difficult (if not impossible) to assess. Established associations between a chronic productive cough and occupational exposures largely derive from general population studies (Axelsson et al. 2016; Doney et al. 2014; Hansell et al. 2014; Jaen et al. 2006; Lange et al. 2003; Sunyer et al. 2005) supported by numerous smaller industry-specific studies (Barber and Fishwick 2008). However, while exposure to vapours, gases, dusts or fumes in the workplace was found to be positively associated with chronic bronchitis in a meta-analysis with odd ratios in the range of 1.2 (1.1;1.4) to 1.4 (1.3; 1.5) (Sadhra et al. 2017), a recent, longitudinal study found that incident chronic bronchitis was not increased in any of these exposure groups (Lytras et al. 2019). Most occupational inhalant exposures have declined substantially in industrialized countries within the last decades (Creely et al. 2007). The improvements are suggested to be ongoing, as a recent study monitoring European industrial minerals sectors between 2002 and 2016 reported a 9% annual decline in respirable dust (Zilaout et al. 2020). Consequently, some work-related inhalant hazards may have reached a level where chronic productive cough is no longer a risk.

Our primary aim was to assess if the established higher risk of chronic productive cough related to occupational exposure to vapours, gases, dusts and fumes is still imminent given the substantial reduction in exposure levels and overall change in the past 40 years.

Methods

Population

The study population (Supplementary Fig. F1) was selected from two Danish population-based cohorts: The Copenhagen City Heart Study and the Copenhagen General Population Study. The first round (1976–78) of the Copenhagen City Heart Study included 14,223 individuals randomly selected from specific areas of Copenhagen. During 1981–83, out of the 14,223 individuals previously enrolled, 11,123 were reexamined, and 1563 new subjects were enrolled. The Copenhagen General Population Study is a cohort initiated in 2003 with continuous follow-up. In both cohorts, all individuals were aged 20 years or older during enrollment. At each visit, the individuals in both cohorts completed a questionnaire, a physical examination, and clinical tests including spirometry.

The studies were approved by Danish Ethical Committees (KF-01-144/01, H-KF-01-144/01) and were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

In the present study, we excluded persons who at study participation were older than 65 years or unemployed the year before (Supplementary Fig. F1). Individuals with missing information regarding chronic productive cough, job title or other covariates were also left out of the analyses.

Chronic productive cough and spirometry

Participants were at every visit asked, "*Do you cough up sputum (in the morning or during the day) for as long as three months every year?*". Questions regarding smoking status and self-reported asthma were also included. Lung function was obtained using spirometry. An electrical spirometer (Model N 403, Monaghan, Littleton, Colorado, USA) was applied in The Copenhagen City Heart Study. In the Copenhagen General Population Study a Vitalograph (Maids Moreton, Buckinghamshire, United Kingdom) was used in the first 14,625 participants and an EasyOne Diagnostic Spirometer (ndd Medizintechnik, Switzerland) in the remaining participants. Both the electrical spirometer and the Vitalograph were calibrated daily, while the EasyOne spirometer was verified with a 3-L syringe regularly. Prebronchodilator forced expiratory volume in the first second of expiration (FEV_1) and forced vital capacity (FVC) were measured with the participant in a standing position. A valid test included at least two measurements which did not differ by more than 5% and a correct visual appearance of the

spirometry curves. The largest volumes of FEV_1 and FVC were recorded.

Occupational inhalant exposure

Job titles and labour market affiliation at the examination date and one year before assessment of outcome were obtained by linkage with the Danish Occupational Cohort with eXposure (DOC*X), a national database involving all wage earners in Denmark with at least one year of employment in the period 1970–2017 (Flachs et al. 2019; Petersen et al. 2019). Each year in the DOC*X database provided information on employment status (employed/not employed) and job codes according to the Danish version of the International Standard Classification of Occupation (DISCO-88). The DISCO-88 codes were linked to an expert-rated job-exposure matrix, the airborne chemical job-exposure matrix (ACE JEM) (Sadhra et al. 2016). The ACE JEM is based upon expert ratings by occupational exposure assessors. It classifies exposure into the type of inhaled pollutant, proportion of workers exposed and intensity (level) of exposure in each of the UK SOC 2000 classification codes (Statistics 2000). Intensities include no exposure, low intensity of exposure (defined as more exposed than the general background occupational level but less than 10% of the U.K. workplace exposure limit), medium and high intensity (equivalent to 10–50% and 50% or higher than the U.K. workplace exposure limit). The proportion of exposed workers within each job code is categorized as < 5%, 5–19%, 20–49% and ≥ 50% of all workers in the specific job code. A complete mapping of the DISCO-88 codes to the UK SOC 2000 was performed. The hierarchy in the UK SOC 2000 differs from DISCO-88, and most of the major and sub-major group codes in the DISCO-88 had no matching SOC 2000 code. JEM values for these were assigned based on the population distribution of the corresponding DISCO-88 unit groups.

Exposure categories for this study were constructed based upon a combination of ACE JEM assigned probability and intensity of exposure. If the ACE JEM assigned the study participant's job at low intensity in more than 5% of workers or medium intensity in 5–49% of workers exposed, it was categorized as low exposure. High exposure was defined as those with medium or high intensity, with at least 50% of workers exposed to the inhalant. The remaining job codes were classified as not exposed. We selected the following, most prevalent exposure types: mineral dust, biological dust, gases & fumes and their composite variable vapours, gases, dusts or fumes (VGDF). VGDF intensity and probability were in the ACE JEM assigned the highest values of the components. The ACE JEM covers working conditions in the U.K. in the period 2000–2013 and does not contain a time axis. As exposure intensities and proportions have declined significantly since the 1970ies, we analyzed the two cohorts separately to investigate time trends in the associations.

Other covariates

Information from the questionnaire was used to categorize study individuals as follows; age (< 50; ≥ 50 years old), smoking (never smoker; former smoker; light smoker < 15 g of tobacco/day; moderate smoker 15– < 25 g of tobacco /day; heavy smoker ≥ 25 g of tobacco /day), highest completed education (elementary school; high school; academic education) and body mass index (BMI). A ratio of pre-bronchodilator forced expiratory volume in 1 s (FEV_1) divided by forced vital capacity (FVC) below 0.70 served as a proxy for chronic obstructive lung disease (COPD). Post-bronchodilator values were not available. Asthma was based on a self-reported doctor-diagnosed asthma.

Statistical analyses

Categorical variables were summarized using numbers and proportions and continuous variables by arithmetic means (standard deviation).

Associations between inhalant occupational exposure the year before study participation and presence of chronic productive cough were examined separately for each cohort using generalized estimating equations (GEE), including both individuals with one and two study visits. The method estimates the population average effect size while accounting for within-subject correlation. The results are presented as odds ratios, OR (95% confidence intervals, CI).

The association of occupational inhalant agents on chronic productive cough interacted with that of smoking (exposure*smoking) and all models were, therefore, stratified by current smoking status (smoker, non-smoker). We adjusted for age, sex, educational level, body mass index in all models, and additionally for smoking status (never or former smoker) in non-smokers and daily tobacco consumption in smokers (light, moderate, heavy smokers). Self-reported asthma and prebronchodilator $FEV_1/FVC < 0.70$ were both possible mediators, confounders and effect modifiers and were tested as independent variables and in interaction analyses.

Sensitivity analyses were performed on the subsample of individuals with two test points to test the strength of the estimates in a design with only repeated measures and in analyses replacing job titles the year before study participation with jobs held at the year of the study examination.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). *P*-values were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics stratified by smoking and participation period are presented in Table 1. The population consisted of 5210 working individuals aged 20–65 from the 1976 to 1983 Copenhagen City Heart Study (CCHS) and 64,279 from the 2003 to 2017 Copenhagen General Population Study (CGPS) with mean baseline ages of 48 (range 21–65) and 50 (20–65) years, respectively. A total of 3096 individuals participated twice between 1976 and 1983, and 7101 between 2003 and 2017 with complete exposure, outcome and covariate data at both visits. Smoking was more prevalent at baseline in the 1976–1983 cohort (68%) than in the 2003–2017 cohort (17%). Smokers more frequently reported chronic productive cough than non-smokers (1976–983 CCHS: 5% of non-smokers, 15% of smokers; 2003–2027 CGPS: 4% of non-smokers, 17% of smokers). The proportion of occupationally exposed was, in general, higher among smokers than non-smokers within the same cohort (Table 2). The occupational inhalant exposure levels at first examination in individuals with two study examinations did not differ from those in the full study population.

Smoking interacted with the association of vapours, gases, dusts or fumes (VGDF) exposure on chronic productive cough ($P < 0.05$ in the 1976–1983 cohort and $P < 0.002$ in the 2003–2017 cohort), and all analyses were therefore stratified by current smoking status. The fully adjusted models stratified by smoking status are presented separately for each cohort in Supplementary Tables S1 and S2. Age above 50 years was strongly associated with chronic productive cough in both cohorts. The odds ratio for chronic productive cough in heavy smokers was approximately 11 times as high as in never smokers. Exposure to mineral dust, biological dust and gases & fumes were greatly overlapping: in 95 percent of observations assigned to high exposure level, exposure to at least two types of exposure contributed (results not shown).

Table 1 Baseline characteristics according to study participation

	Period 1 (1976–1983) ($N = 5210$)	Period 2 (2003–2017) ($N = 64,279$)
Age, years	48 (21–65)	50 (20–65)
Male sex	2861 (55)	28,235 (44)
Smoking status		
Never	887 (17)	28,877 (45)
Former	804 (15)	24,407 (38)
Light smoker	1344 (26)	5159 (8)
Moderate smoker	1600 (31)	4606 (7)
Heavy smoker	575 (11)	1230 (2)
Education		
Elementary	3425 (66)	7527 (12)
High school	1513 (29)	38,584 (60)
Academic	266 (5)	18,040 (28)
BMI, kg/m^2	24.7 (3.9)	25.9 (4.3)
Pulmonary findings		
Self-reported asthma	88 (2)	3886 (6)
FEV_1, liters	2.9 (0.8)	3.3 (0.8)
FVC, liters	3.5 (1.0)	4.3 (1.0)
FEV_1/FVC	0.8 (0.1)	0.8 (0.2)
FEV_1/FVC < 0.70	663 (13)	6781 (11)

N number of individuals, *BMI* body mass index, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity. Data are presented as number (range), number (%) or mean (standard deviation)

Table 2 Occupational exposure at first examination according to period and smoking status

	Period 1 (1976–1983)		Period 2 (2003–2017)	
	Non-smoker	Smoker	Non-smoker	Smoker
Vapours, gases, dusts or fumes				
No	805 (48)	1407 (40)	36,250 (68)	6572 (60)
Low	611 (36)	1444 (41)	13,008 (24)	2812 (25)
High	275 (16)	668 (19)	4026 (8)	1611 (15)
Mineral dust				
No	1228 (72)	2411 (69)	43,941 (82)	8603 (78)
Low	317 (19)	763 (22)	7301 (14)	1420 (13)
High	146 (9)	345 (10)	2042 (4)	972 (9)
Biological dust				
No	1357 (80)	2788 (79)	44,794 (84)	9114 (83)
Low	266 (16)	559 (16)	7909 (15)	1665 (15)
High	68 (4)	172 (5)	581 (1)	216 (2)
Gases & fumes				
No	1492 (88)	2990 (85)	50,016 (94)	9947 (90)
Low	145 (9)	402 (11)	2342 (4)	660 (6)
High	54 (3)	127 (4)	926 (2)	388 (4)

Data are presented as number (%)

Occupational inhalant exposures and chronic productive cough

Associations between occupational inhalant exposures and chronic productive cough are shown in Table 3. In smokers, high levels of all types of exposure except for biological dust in the 1976–1983 cohort were associated with chronic productive cough with odds ratios ranging from 1.2 to 1.6. In addition, odds ratios in non-smokers in the 1976–983 cohort largely resembled those of smokers, but only high levels of vapours, gases, dusts or fumes (VGDF) and low levels of mineral dust in non-smokers reached statistical significance with odds ratios of 1.5 (95% CI 1.0;2.3) and 1.7 (1.1;2.4), respectively. No tendencies or significant associations were found in non-smokers from 2003 to 2017.

Table 3 Odds ratios for chronic productive cough and exposure according to period and smoking status

	Period 1 (1976–1983)		Period 2 (2003–2017)	
	Non-smoker	Smoker	Non-smoker	Smoker
Vapours, gases, dusts or fumes				
Low	1.2 (0.8;1.7)	0.9 (0.8;1.1)	1.0 (0.9;1.1)	1.1 (1.0;1.3)
High	1.5 (1.0;2.3)	1.3 (1.1;1.6)	1.0 (0.9;1.1)	1.3 (1.1;1.5)
Mineral dust				
Low	1.7 (1.1;2.4)	1.1 (0.9;1.3)	1.0 (0.9;1.1)	0.9 (0.8;1.1)
High	1.5 (0.9;2.5)	1.6 (1.3;1.9)	1.1 (0.9;1.3)	1.2 (1.0;1.4)
Biological dust				
Low	1.0 (0.6;1.5)	0.9 (0.7;1.1)	0.9 (0.8;1.1)	1.2 (1.0;1.3)
High	1.4 (0.7;2.9)	1.2 (0.9;1.6)	1.2 (0.9;1.6)	1.5 (1.1;2.0)
Gases & fumes				
Low	1.0 (0.6;1.6)	0.9 (0.7;1.1)	0.9 (0.8;1.1)	1.0 (0.9;1.3)
High	0.6 (0.2;1.5)	1.6 (1.2;2.1)	1.1 (0.9;1.4)	1.3 (1.0;1.6)

Generalized estimating equations on exposure and chronic productive cough. All odds ratio (95% confidence interval) are adjusted for age group, sex, body mass index, and educational level, and additionally for smoking status (never or former smoker) in non-smokers and daily tobacco consumption in smokers (light, moderate, heavy smokers). Reference is non-exposed to the category of exposure

The most prevalent occupations in the 2003–2017 cohort did not differ between smokers and non-smokers but varied across exposure categories. Construction and maintenance labourers, and helpers and cleaners were the most prevalent occupations exposed to high levels of mineral dusts; carpenters and joiners and building construction labourers the most frequent in high-level biological exposure, and cooks and motor vehicle mechanics and fitters in high-level gases & fumes exposure.

Stratification by or adjusting for asthma and FEV_1/FVC < 0.70 did not markedly alter the main associations. No significant interactions on chronic productive cough were found between occupational inhalant exposure and sex, exposure and self-reported asthma or exposure and FEV_1/FVC < 0.70 (data not shown).

Sensitivity analyses

Restricting the population to individuals with repeated measurements did not change the direction of any of the statistically significant associations (Supplementary Table S3). High levels of all exposure types except gases & fumes were associated with chronic productive cough in non-smokers from 1976 to 1983. We were not able to conduct the analyses on the subtypes of exposure in smokers from 2003 to 2017 due to too few exposed individuals.

We stratified the study populations into two smoking categories (non-smoker and smoker). All models were repeated with three smoking groups (never smokers, former smokers, current smokers), which showed similar associations of occupational inhalant exposure in chronic productive cough in former and never smokers and with no overall change in our conclusions.

To make sure that the exposure preceded the outcome we used the individuals' job title in the year prior to the examination., All models were also run with exposure from the job title from the actual year of study participation with no change in the main findings.

Discussion

In this study, high levels of work-related mineral dust, biological dust, gases & fumes and the composite variable vapours, gases, dusts or fumes were associated with chronic productive cough in smokers in both 1976–83 and 2003–2017, with high levels of biological dust borderline significant among smokers in the 2003–2017 cohort. In the 1976–1983 cohort only, the same tendencies were found in non-smokers. In total, chronic productive cough was prevalent in 4% of non-smokers and 17% of smokers. Smoking status and intensity were strongly associated with chronic productive cough as an indication of the validity of study design and data.

A recent meta-analysis of job exposure matrix-based studies showed odds ratios for chronic bronchitis and exposure to either vapours, gases, mineral or biological dust or fumes within the range of 1.2–1.6 (Sadhra et al. 2017), which is in line with our findings in smokers. The meta-analysis was based on both general population and work-based studies with a time of exposure ranging from 1960 to 2010. Exposure to high but not low levels of the composite variable vapours, gases, dusts or fumes (VGDF) was associated with chronic bronchitis in both the meta-analysis and our study.

General population cohorts with longitudinal data on chronic productive cough and occupational inhalant exposures, which are based on different cohorts are few (Krzyzanowski and Jedrychowski 1990; Lytras et al. 2019; Skorge et al. 2009). A recent analysis of the incidence of chronic bronchitis according to occupational exposures (Lytras et al. 2019) found that none of the selected inhalant exposures were associated with incident chronic bronchitis in comparable age groups to the present study. The study was initiated in 1991–1993 and followed-up around the year 2000 and/or 2010. Possible exposure was recorded up to several years prior to the outcome. Chronic productive cough is, in many cases, dependent on the presence of the trigger (Allinson et al. 2016). Studies have shown that chronic bronchitis resolves in the majority of smokers who quit smoking (Brown et al. 1991; Lange et al. 1990a) and in half of these within one month (Wynder et al. 1967). Even in patients

with mild to moderate chronic obstructive pulmonary disease, changes in respiratory symptoms generally occurred within the first year after quitting smoking (Kanner et al. 1999). The different results found by (Lytras et al. 2019) might be explained by way of assessing exposure. In addition, the study did not stratify based on smoking status, which might contribute to the observed differences.

Also in support of our findings, a study by (Zock et al. 2001) based on the same cohort as mentioned above but with only cross-sectional data and exposure primarily defined by current occupation found no association between chronic productive cough and exposure to vapours, gases, dusts or fumes in never- or ex-smokers, but a prevalence ratio of 1.3 (0.9;1.8) and 1.7 (1.2;2.4) in current smokers exposed to low and high levels of VGDG respectively (Zock et al. 2001).

Our study suggests that some exposures in 2003–2017 are too weak to be associated with chronic productive cough without the presence of another irritant like cigarette smoking. In our study, only a small proportion of non-smokers in the 1976–1983 cohort were occupationally exposed, and the insignificant results among non-smokers may therefore alternatively be explained by lack of power. High levels of biological dust were only borderline significant in smokers in the 1976–1983 cohort, which is most likely due to lack of power as well. The odds ratios in exposed smokers in the 1976–1983 cohort were marginally higher than in the contemporary 2003–2017 cohort as expected due to higher levels of occupational inhalant exposure at the workplace in 1976–1983 compared with 2003–2027 (Creely et al. 2007). The job-exposure matrix was, however, not designed to access exposures before the year 2000, and non-exposed job titles today might have been exposed in 1976–1983, causing misclassification with a weakening of the 1976–1983 findings. The observed associations in both cohorts could be due to unmeasured confounding unequally distributed between smoking status and exposure group. Occupationally exposed individuals may also have been exposed to traffic pollution and passive smoking. However, all individuals lived in Copenhagen, which minimizes possible differences in air pollution. We were not able to control for passive smoking. Yet, our main findings were related to the group of current smokers in whom secondhand smoking plays a less important role than in non-smokers. Chronic productive cough is correlated with gastroesophageal reflux syndrome and rhinosinus disease (Caminha et al. 2018; Hakansson et al. 2013; Ingebrigtsen et al. 2015), both independently associated with smoking. Yet, it is not likely that the extent of these differ between exposed and non-exposed. In our study, the odds ratio of chronic productive cough was slightly higher in former smokers than in never smokers, similar to prior findings (Brown et al. 1991; Lange et al. 1990a).

Self-reported asthma was more frequently reported in 2003–2017 reflecting an overall increase in the prevalence of asthma (Browatzki et al. 2009; Sears 2014). Asthma and airflow limitation ($FEV_1/FVC < 0.70$, which was our proxy for chronic obstructive lung disease) were both positively associated with a chronic productive cough but adjusting for or stratifying by these variables gave similar results. Also, we did not find any interactions of asthma or airflow limitation with occupational inhalant exposure on risk of chronic productive cough. Consequently, we did not consider asthma or FEV_1/FVC to be important mediators, confounders or effect modifiers.

All statistically significant main findings were within the range of odds ratios of 1.2 and 1.7. In comparison, being a light smoker increased the odds ratio of chronic productive cough to approximately 3, and heavy smoking to 10–13 (results not shown). Despite the different magnitudes of associations, chronic productive cough as a result of occupational exposures is important to detect and subsequently prevent. In some countries, regular lung function testing is mandatory in workers exposed to selected inhalant hazards (Hochgatterer et al. 2013). The standard test is spirometry, which is highly dependent on both the patient and the examiner, and even when conducted correctly, it is relatively insensitive to detect short-term differences (Hnizdo et al. 2006; Townsend 2000). Furthermore, a more rapid decline in lung function is not an obligate finding in all lung diseases, in particular not in asthma. Surveillance of new-onset chronic productive cough in exposed jobs might be an alternative. It is difficult to distinguish between chronic productive cough caused by cigarette smoking combined with occupational inhalant exposure as opposed to cigarette smoking alone. Nonetheless, chronic productive cough is associated with permanent lung damage such as accelerated lung function decline (Vestbo et al. 1996) and might pose a warning.

Strengths of our study include the large samples of randomly selected individuals separated in time, enabled assessment of period effects. The research question was not known to the participants, thereby minimizing over-reporting of the outcome by potentially concerned, exposed workers. Exposure was not self-reported, reducing the risk of recall and reporting bias. A proportion of our population had repeated measurements enabling generalized estimating equation , taking account of the correlation between successive measurements on the same individual.

The study has limitations. The use of a job-exposure matrix causes misclassification also in the contemporary cohort. The traditional way of assessing occupational inhalant exposure is personal or area sampling of specific substances, but such information is sparse and generally restricted to high-risk occupations. Job exposure matrices do not reflect the variation in exposure levels within a given occupation and person. Therefore, studies based upon JEMs will provide risk estimates for a narrower range of exposures

than studies based on individual assessments. However, risk estimates characterizing the actual contrast may not be biased depending on the type of error (Armstrong 1998).

Data on job titles were not complete from the DOC*X database and improved with time. In the 1980′ies, around 20% of the participants had missing job titles either due to unemployment, early retirement or lacking job titles from registers, and these individuals were excluded from all analyses. Temporality is a concern since our design did not ensure that exposure preceded the outcome. Unfortunately, data were not available to perform prospective data analysis. We did not know when participants started or stopped coughing, which did not allow us to study the influence from entering or exiting jobs with occupational inhalant exposures. In addition, individuals might change careers where the risk of exposure to inhaled pollutants is lower, i.e. adjustment to enable continued working. We were not able to identify the participants who experienced chronic productive cough secondary to other factors such as gastroesophageal reflux or rhinosinusitis. The exposed workers in this cohort generally derived from a lower socio-economic status than the unexposed group. To reduce the risk of bias, we controlled for the longest obtained education. The FEV_1/FVC ratio was based on spirometry performed at different time periods and with different equipment. Direct comparison was not possible as the spirometers stopped functioning. Any differences were, however, assumed to affect the unexposed and exposed individuals equally and were within the Copenhagen City Heart Study estimated to be minor (Lokke et al. 2013). Our population was predominantly middle-aged, and the results cannot without caution be extrapolated to younger age groups. Individuals returning to a cohort study are generally healthier than those who do not. The individuals of our study, with only one observation, were primarily part of the cohort still enrolling participants, and many of them had not yet been invited to a follow-up visit. The differences might, therefore, not be as large as could be expected. Baseline exposure, baseline chronic productive cough and baseline FEV_1/FVC did not differ between individuals with multiple visits and those individuals who only participated once in our studies.

In conclusion, selected occupational inhalant exposures were associated with chronic productive cough in two cohorts of the general population. Whereas this association was observed in both smokers and non-smokers in a 1976–83 cohort, it was only apparent in smokers in the 2003–2017 cohort.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval The cohort studies were approved by Danish Ethical Committees (KF-01-144/01, H-KF-01-144/01).

Consent to participate The cohort studies were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

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RESEARCH ARTICLE

Occupational exposures and exacerbations of asthma and COPD—A general population study

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Abstract

Purpose

Recent studies suggest that occupational inhalant exposures trigger exacerbations of asthma and chronic obstructive pulmonary disease, but findings are conflicting.

Methods

We included 7,768 individuals with self-reported asthma (n = 3,215) and/or spirometric airflow limitation (forced expiratory volume in 1 second (FEV_1)/ forced expiratory volume (FVC) <0.70) (n = 5,275) who participated in The Copenhagen City Heart Study or The Copenhagen General Population Study from 2001–2016. Occupational exposure was assigned by linking job codes with job exposure matrices, and exacerbations were defined by register data on oral corticosteroid treatment, emergency care unit assessment or hospital admission. Associations between occupational inhalant exposure each year of follow-up and exacerbation were assessed by Cox regression with time varying exposure and age as the underlying time scale.

Results

Participants were followed for a median of 4.6 years (interquartile range, IQR 5.4), during which 870 exacerbations occurred. Exacerbations were not associated with any of the selected exposures (high molecular weight sensitizers, low molecular weight sensitizers,

Denmark: http://www.dst.dk/en/OmDS/organisation/. Data from the two cohorts, the Copenhagen City Heart Study and the Copenhagen General Population Study may be available for researchers who meet the criteria for access to confidential data. Contact information can be found at https://www.frederiksberghospital.dk/afdelinger-og-klinikker/oesterbroundersoegelsen/kontakt/Sider/default.aspx#10 and https://www.herlevhospital.dk/afdelinger-og-klinikker/klinisk-biokemisk-afdeling/forskning/Sider/Herlev-oesterbroundersoegelsen.aspx.

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irritants or low and high levels of mineral dust, biological dust, gases & fumes or the composite variable vapours, gases, dusts or fumes). Hazards ratios ranged from 0.8 (95% confidence interval: 0.7;1.0) to 1.2 (95% confidence interval: 0.9;1.7).

Conclusion

Exacerbations of obstructive airway disease were not associated with occupational inhalant exposures assigned by a job exposure matrix. Further studies with alternative exposure assessment are warranted.

Introduction

Globally, asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent and common causes of morbidity and mortality [1–3]. While airflow limitation and inflammation in asthma may resolve spontaneously or in response to medication, airway obstruction in COPD is, by definition, persistent. Asthma involves the large and small airways, whereas COPD is a disease primarily in the small airways. The two conditions are overlapping. Patients with asthma might develop chronic airway obstruction, and elements of reversible airflow limitation are often present in COPD [4–6].

Exacerbations are acute worsening of asthma or COPD and are often defined on the basis of management: treatment with oral corticosteroids and antibiotics in an outpatient setting (moderate exacerbations), or managed in emergency care with or without hospital admission (severe exacerbations) [7–9]. Exacerbations are associated with an accelerated loss of lung function among some asthmatic patients [10] and decreased survival in patients with COPD [11, 12]. Possible triggers of exacerbations of asthma and COPD include infections, low temperatures and exposure to different types of airborne particles [13, 14]. Airborne particles include ambient air pollution with well-described associations to exacerbations of COPD [15] and asthma [16–18], and occupational inhalant exposures with much less evident associations. Occupational studies have largely focused on new-onset asthma or COPD [19–22]. It is, however, possible that workplace hazards are associated with exacerbations of asthma and COPD, and that these may cause greater morbidity [23]. Exacerbations of both diseases might be associated with the same inhalant hazards at work but are rarely studied together. Recent studies suggest that different types of inhalant exposures in the workplace are associated with exacerbations of asthma [24] and COPD [25], but rely on self-reported exacerbations which are prone to recall bias. Updated information on the risk of exacerbations is important for evidence-based guidance of asthma and COPD patients in general.

We studied the association between concurrent inhalant occupational exposures and exacerbations of asthma and/or COPD.

Methods

Population

Participants were selected from two large cohort studies: The Copenhagen City Heart Study (CCHS) [26] and The Copenhagen General Population Study (CGPS) [27]. CCHS was initiated in 1976, and the fifth round of follow up was completed in 2015. CGPS started in 2003 and is a prospective cohort study with ongoing recruitment of participants. Individuals from the fourth (2001–2003) and/or the fifth (2011–2015) follow up round of CCHS and from

2003–2016 in the CGPS were eligible for the present study. Participants in both studies were 20–100 years old and had been randomly selected from the general population through the Danish Civil Registration Service. All participants gave written informed consent, and both studies were approved by the Danish Ethics Committees. All data were fully anonymized before assessment. At each round of examination, participants filled out a questionnaire, and completed a physical examination at a test center located at a public hospital in Copenhagen. The questionnaire was self-administered, concerning health status, lifestyle and socio-economic status, and was assessed by one of the investigators on the day of attendance. The physical examination included spirometry. Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured by investigators and repeated three times with the participant in a standing position. The test was redone if the two closest trials differed by more than 5%, or the visual appearance of the spirometry tracing was unsatisfactory. A Vitalograph spirometer (Maids Moreton, Buckinghamshire) was used in The Copenhagen City Heart Study and by the first 14,624 individuals in the Copenhagen General Population Study, while an EasyOne Diagnostic Spirometer (ndd Medizintechnik, Switzerland) measured lung function in the remaining individuals.

Individuals were included in the present study, if they reported asthma in the questionnaire and/or had spirometry indicating airflow limitation (FEV_1/ FVC < 0.70). Other inclusion criteria in the present study were age 30–60 years at baseline, employment at least one year during the study period, and complete data regarding smoking habits, education, weight, height and spirometry.

A sample of individuals with no reported asthma and with $FEV_1/FVC \geq 0.70$ was constructed to test for differences in baseline exposure. A one-to-three matching was conducted based on age at inclusion, sex, smoking status (never, former, current smoker), BMI category (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m2), education (elementary, high school, academic) and participation after the year 2000.

Exposure

We combined job codes from the Danish Occupational Cohort database (DOC*X) [28] with job exposure matrices to determine exposure each year of the follow-up period (S1 Table). DOC*X is a database with annual job titles according to the Danish version of the International Standard Classification of Occupation (DISCO-88) on all Danish wage earners from 1970 until present. For the participants with complete job histories, exposure status was relatively stable during employed year of follow up. In case of missing job codes in employed years, prior job titles maximally five years prior were extrapolated. We applied parts of two expert-rated job exposure matrices; the Airborne Chemical Job Exposure Matrix (ACEJEM) [29] commonly used for chronic obstructive lung disease, and the Occupational Asthma-specific JEM (OAsJEM) [30] designed for occupational asthma. The ACE JEM was developed for the UK SOC 2000 classification job codes, the OAsJEM for the International Standard Classification of Occupation (ISCO-88), and both were converted into DISCO-88 codes. The ACE JEM included information on 12 pollutant types (including composites) and assigned proportion of exposed workers (<5%, 5–19%, 20–49%, ≥50%), level of exposure (not exposed, low, medium, high) and a binary variable (non-exposed, exposed) to each job code. The OAsJEM covered 30 different sensitizers or irritants, and each job code was classified in three categories: high ("at least 50% of the workers exposed and moderate to high intensity"), medium ("low to moderate probability or low intensity of exposure, such as 'high probability and low intensity' or 'low probability and moderate to high intensity'") and not exposed ("unlikely to be exposed with low probability and low intensity").

To achieve adequate power we selected the following main types of exposure: mineral dust, biological dust, gases & fumes and the composite variable of vapours, gases, dusts or fumes (VGDF) from the ACE JEM, and high molecular weight sensitizers, low molecular weight sensitizer and irritants from the OAsJEM. Probability and intensity of exposure assigned by the ACEJEM were combined into the following classes: no, low and high exposure (S2 Table). Exposure in the OAsJEM was dichotomized into exposed (including high and medium exposure assigned by the OAsJEM) and unexposed.

Outcome

Exacerbations were defined by treatment with oral corticosteroids, emergency care unit assessment (emergency care) or hospital admission related to asthma or COPD. Cases were identified through linkage with The Danish National Prescription Registry [31] and The Danish National Patient Register [32]. Treatment with oral corticosteroids included prescriptions for prednisolone (ATC code H02AB06) or prednisone (H02AB07). Emergency care or hospital admissions comprised of the following: (1) primary diagnosis "chronic obstructive pulmonary disease" (ICD-code J44) and secondary diagnosis "pneumonia" (J13 to J18) or (2) primary diagnosis "asthma" (J45) or "status asthmaticus" (J46) or (3) primary diagnosis "respiratory failure" (J96) in combination with a secondary diagnosis "chronic obstructive pulmonary disease" (J44) or "asthma" (J45) or "status asthmaticus" (J46). The highest level of treatment per episode was recorded, and the date of prescription, emergency care or hospital admission day denoted an event. Exacerbations one year prior to inclusion were recorded separately. In case of an exacerbation occurring before inclusion and less than four weeks before an event in the follow-up period, the event was regarded as an exacerbation in the previous year.

Covariates

Based upon status at inclusion, the following covariates were included; sex, smoking status (never, former, current smoker), BMI category ($<$18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), education (elementary, high school, academic), FEV_1% predicted class ($<$80% and $\geq$80%) and exacerbations one year prior to study inclusion (none, $\geq$1). Calculation of FEV_1% predicted has previously been described [33].

Statistics

In a follow-up design, we used Cox regression with time-varying exposure to examine the hazard ratio (HR) of exacerbation according to inhalant exposure. Age was the underlying time scale, and end of follow-up was the first occurring exacerbation, exit from the labour market, death or year 2017, whichever came first. We found no interactions between the effects of exposure and sex, exposure and smoking status, exposure and FEV_1% predicted or exposure and exacerbations one year prior to inclusion. Stratifying by exacerbation within the year before inclusion or excluding the covariate from the model did not change main findings. We conducted sensitivity analyses including only self-reported asthma, $FEV_1/FVC<0.70$ or individuals with a complete job history. To ensure temporality between exposure and outcome we repeated all analyses with inhalant exposure assigned the previous year of all follow-up years. Collinearity of exposures did not allow for analyses including more than one type of exposure in a model. Proportional hazards assumptions were evaluated graphically. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses. P-values were two-sided, and statistical significance was defined as $p<0.05$.

Results

A total of 7,768 individuals with self-reported asthma, $FEV_1/FVC<0.70$ or a combination of the two were included. The mean age at study inclusion was 50 years (standard deviation, SD 7), and 62% were current or former smokers (Table 1).

Exposure to the selected inhalant agents at study inclusion varied from 28% exposed to low levels of vapours, gases, dusts or fumes (VGDF) to 2% exposed to high levels of biological dust and gases & fumes (Table 2). At the time of study inclusion, 61% of the population (N = 4,736) was not exposed to any of the selected inhalant agents. Proportions of exposed in the matched population with no self-reported asthma and $FEV_1/FVC \geq 0.70$ resembled our population (S3 Table).

First time exacerbation since study inclusion was recorded in 870 individuals during a median of 4.6 years (interquartile range, IQR 5.4). The number of exacerbations was 411 among individuals with self-reported asthma only, 317 in the group of participants with $FEV_1/FVC < 0.70$ only, and 142 in the remaining participants. Only 8% of the exacerbations involved emergency care or hospital admission. Exacerbations were associated with low FEV_1 at inclusion; HR 1.5 (95% confidence interval [CI] 1.3;1.8), a body mass index above normal at

Table 1. Characteristics of the study population at inclusion.

	N = 7,768
Age, years, mean (SD)	50 (7)
Sex, male, n(%)	
Male	3,361 (43)
Female	4,407 (57)
BMI, n(%)	
<18.5	54 (1)
18.5–24.9	3,716 (48)
25–29.9	2,869 (37)
≥30	1,129 (15)
Education, n(%)	
Elementary	672 (9)
High school	4,774 (61)
Academic	2,322 (30)
Smoking, n(%)	
Never smoker	2,984 (38)
Former smoker	3,083 (40)
Current smoker	1,701 (22)
Self-reported asthma, n(%)	3,215 (42)
$FEV_1/FVC < 0.70$, n(%)	5,275 (68)
Self-reported asthma and FEV1/FVC <0.70, n(%)	722 (9)
FEV_1% predicted, n(%)	
≥80%	5,806 (75)
<80%	1,962 (25)
Exacerbations one year prior to inclusion, n(%)	
No	7,562 (97)
≥ 1	206 (3)

Abbreviations; SD: standard deviation; n: number; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

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Table 2. Exposures at study inclusion.

	Exposure, number (row-%)		
	Unexposed	**Low**	**High**
ACE JEM			
Vapors, gases, dusts or fumes	4,906 (63)	2,184 (28)	678 (9)
Mineral dusts	6,167 (79)	1,189 (15)	412 (5)
Biological dusts	6,368 (82)	1,276 (16)	124 (2)
Gases&fumes	7,236 (93)	352 (5)	180 (2)
	Unexposed	**Exposed**	
OAsJEM			
High molecular weight sensitizer	6,739 (87)	1,029 (13)	
Low molecular weight sensitizer	6,633 (85)	1,135 (15)	
Irritants	5,889 (76)	1,879 (24)	

Abbreviations: ACE JEM: The Airborne Chemical Job Exposure Matrix; OAsJEM: The Occupational Asthma-specific JEM

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inclusion; HR for BMI 25–29.9: 1.3 (95% CI: 1.1;1.5); HR for BMI≥30: 1.5 (95% CI 1.3;1.9) and female sex; HR 1.5 (95% CI 1.3;1.8) (S4 Table). Having had an exacerbation in the year before inclusion (n = 206) was associated with a hazard ratio of 6.9 (95% CI 5.6;8.5) of a new exacerbation.

Main results are presented in Table 3. We found no associations between exacerbations and mineral dust, biological dust, gases & fumes, vapours, gases, dusts or fumes (VGDF), high molecular weight sensitizer (HMW), low molecular weight sensitizer (LMW) or irritants. Analyses on self-reported asthma only (S5 Table) or $FEV_1/FVC < 0.70$ (S6 Table) showed similar results except for exposure to low levels of gases & fumes which was associated with a hazard ratio of 1.6 (95% CI 1.1;2.3). Repeating the analyses with exposure assigned one year prior, excluding FEV_1% predicted as a covariate or only including individuals with a complete job history did not change our main findings.

Discussion

Our study is the first to comprehensively assess the association between exacerbations and inhalant occupational hazards in a large population of individuals from the general population with self-reported or spirometric measures indicating asthma or COPD. An exacerbation was recorded in 870 out of 7,768 individuals with self-reported asthma and/or airflow limitation during a median follow-up of 4.6 years (interquartile range, IQR 5.4). In line with findings from clinical cohorts of patients with asthma and COPD, the exacerbation risk was significantly higher in individuals with low lung function and a history of previous exacerbations. There was no association between occupational inhalant exposures and exacerbations. Including only individuals with self-reported asthma or participants with airflow limitation did not alter the results, apart from the observation that low levels of gases & fumes were associated with exacerbations in individuals with self-reported asthma.

The strong association between prior exacerbations and future events is well-established [34, 35]. In our population of individuals with self-reported asthma, 4% exacerbated within the first 12 months of follow-up, and 6% of these were defined by a hospital admission or emergency care. In line with this, a large study of patients with asthma with similar ages and access to health care who received at least one type of asthma medication reported that within 12 months 8% exacerbated and 16% of these required hospital admissions or emergency care in

Table 3. Associations between inhalant exposures and exacerbations.

	Exacerbations	Follow-up years	Crude	Adjusted*
	Number	*Number*	*HR (95% CI)*	*HR (95% CI)*
Vapors, gases, dusts or fumes				
No	553	26.340	1 (ref)	1 (ref)
Low	222	11.683	0.9 (0.8;1.1)	1.0 (0.8;1.1)
High	78	3.508	1.1 (0.9;1.4)	1.0 (0.8;1.3)
Mineral dusts				
No	692	33.244	1 (ref)	1 (ref)
Low	114	6.133	0.9(0.8;1.1)	1.0 (0.8;1.2)
High	47	2.154	1.1(0.8;1.4)	1.0 (0.7;1.3)
Biological dusts				
No	709	34.031	1 (ref)	1 (ref)
Low	132	6.841	0.9 (0.8;1.1)	0.9 (0.7;1.0)
High	12	660	0.9 (0.5;1.6)	0.8 (0.5;1.5)
Gases&fumes				
No	792	38.811	1 (ref)	1 (ref)
Low	42	1.706	1.1 (0.8;1.5)	1.2 (0.9;1.7)
High	19	1.015	1.0 (0.7;1.5)	0.9 (0.5;1.4)
High molecular weight sensitizer				
Unexposed	747	35.978	1 (ref)	1 (ref)
Exposed	106	5.554	0.9 (0.8;1.1)	0.8 (0.7;1.0)
Low molecular weight sensitizer				
Unexposed	723	35.619	1 (ref)	1 (ref)
Exposed	130	5.913	1.1 (0.9;1.3)	1.0 (0.8;1.2)
Irritants				
Unexposed	632	31.861	1 (ref)	1 (ref)
Exposed	221	9.671	**1.1 (1.0;1.3)**	1.0 (0.9;1.2)

Cox regression with time varying exposure and age as underlying time scale *Adjusted for sex, education, smoking status, body mass index and FEV_1% predicted. Abbreviations; HR: hazard ratio; CI: confidence interval.

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the UK [34]. A possible explanation for the slightly lower occurrence in our study is that our definition of asthma did not require the use of asthma medication thereby including milder and inactive cases.

Exacerbations of asthma and COPD have been studied separately in recent occupational studies, and results of one study are partly in agreement with our findings [24], whereas others are not [25, 36]. Consistent with our results, JEM assigned exposure to agents with high molecular weight, low molecular weight or irritating properties were not associated with exacerbations treated by oral corticosteroids or requiring emergency treatment or hospital admission [24]. Self-reported exposure to biological dust and the composite variable gas, smoke or dust but not mineral dust was, however, positively associated with exacerbations requiring emergency care treatment or hospital admission, but not to exacerbations controlled by corticosteroids alone. In another study, asthma exacerbations were associated with high and low levels of biological dust and high and not low levels of mineral dust, gases and fumes and a composite variable [36]. In a population of current or former smokers with COPD, intermediate/high risk of exposure in the longest-held job was associated with exacerbations requiring health care utilization with low risk of exposure as a reference [25].

The diverging results might overall be explained by different ways of assessing exacerbations and exposure or the chosen covariates. In all studies mentioned above, exacerbations were self-reported and thereby susceptible to recall bias. Exposure was accounted for differently; not required to be concurrent with exacerbations [25] or the reported significant findings were based on self-reports [24]. We adjusted for body mass index (BMI) and education as a proxy of socioeconomic position. Both have been shown to be directly or indirectly associated with exacerbations of asthma [37–39] and possibly correlated with occupational exposure. The two studies concerning exacerbations of asthma [24, 36] did not control for these which might contribute to the different findings.

Our results suggest that exposure to the selected inhalant hazards is not associated with exacerbations in individuals with airway obstruction who are able to continue to work. Improved technology and governmental regulation are important contributors to a large decrease in most occupational inhalant exposures since the 1970s [40] making findings plausible. Traditionally, asthma and COPD have not been studied together in the occupational setting. However, the diseases are overlapping and difficult to distinguish between solely based on data available in our cohorts. Even in studies with access to post-bronchodilator pulmonary function data, reversibility was found in 44–50% of patients with COPD [41, 42], and 25% of asthma patients aged 55 or older had a co-existent diagnosis of COPD [43]. In analyses restricting the population to self-reported asthmatics, we found that low levels of gases & fumes were associated with exacerbations with a hazard ratio of 1.6 (1.1;2.3). The finding might be explained by multiple testing, but is biologically plausible, as asthma exacerbations are also associated with outdoor ambient particulate matter [44]. Regardless, our finding needs to be replicated in other studies.

Strengths of the study included register-based job titles year by year, securing concurrent exposure. Exacerbations were identified in registers and not prone to recall bias. The population represented a wide range of the general population enabling analyses of exposed or unexposed individuals with the same educational level as a proxy of socioeconomic position. Exposure rates were comparable to a matched group of controls.

Our study has limitations. The population was selected by a self-reported diagnosis of asthma or spirometry indicating airflow limitation. A large proportion of individuals with FEV_1/FVC below 0.70 was never smokers in the present study. Some of these may have undiagnosed asthma. However, a study with post-bronchodilator spirometry reported similar findings among never smokers [45]. In total, 312 exacerbations occurred among individuals with $FEV_1/FVC<0.70$ and no self-reported asthma, and 24% (74/312) of these among never smokers suggesting that this group of individuals were indeed ill. Exposure was assigned by job exposure matrices (JEM), which inevitably causes misclassification, as JEMS do not account for variations in levels of exposure within jobs or at the individual level. However, if the mean exposure level for a given job is accurate, this misclassification is not likely to result in attenuated risk estimates, because the measurement error is of Berkson type [46]. We do acknowledge that validation studies for the applied JEMS are not available, and therefore non-differential misclassification towards zero cannot be ruled out. The occupational airborne chemical exposure matrix (ACE JEM) [29] and the occupational asthma-specific JEM (OAs-JEM) [30] were created with an emphasis on detecting new-onset asthma and COPD rather than exacerbations. The selected categories of exposure were, however, considered to be possible occupational triggers of exacerbations of COPD and asthma. We were not able to account for the use of respiratory protective equipment (RPE), as this was not included in the ACE JEM or in the questionnaire. Legislation in Europe introduced in the 1980s has focused on adjustment of use of RPE as well as assessing its effectiveness, and thus RPE is now considered a last resort of protection. Exacerbations were identified by prescription for oral

corticosteroids, which are also prescribed for other diseases such as rheumatoid arthritis and inflammatory bowel disease. Yet, the method has previously been validated and is generally accepted [47], and the risk of bias is considered non-differential. Finally, we did not control for ambient air pollution, as our population was urban. Our population was relatively young, and we did not adjust for comorbid disease. We did not have information on atopy, which may play a role in asthma exacerbations, but its role in late-onset asthma is considered small [48]. Our study population is not representative of all patients with airflow limitations. The mean age at inclusion was 50 years old, and the median follow-up time was 4.6 years. Traditionally, COPD was considered a disease of those aged >50 years, but is suggested to be detectable in 20–45 year old individuals [49]. Still, our population is young. As concomitant exposure was essential in our study, we did not include older participants. Only 9% of the participants reported elementary school as highest level of education. The corresponding rate in the general population aged 35–65 years old in the capital region of Denmark in 2008 was 21% [50] and 24% in the first round of examinations in The Copenhagen General Population Study. A possible explanation for the lower frequency in our population is that the overall lower employment rates among individuals with asthma and COPD are most pronounced in lower educational levels [51–53]. Consequently, power in the present study may be affected.

In conclusion, our results indicate that occupational exposures in Danish individuals who continue to work despite asthma and COPD are not associated with a higher risk of exacerbations.

Supporting information

S1 Table. Overview of the methodology.
(DOCX)

S2 Table. Exposure classes combining level and proportion of exposure assigned by the Airborne Chemical Job Exposure Matrix.
(DOCX)

S3 Table. Exposure at study inclusion in study population and matched group.
(DOCX)

S4 Table. Full Cox regression model with time varying exposure and age as underlying time scale.
(DOCX)

S5 Table. Associations between exposure and exacerbations of self-reported asthma.
(DOCX)

S6 Table. Associations between selected inhalant hazards and exacerbations in individuals with FEV1/FVC<0.70.
(DOCX)

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Original article

Occupational inhalant exposures and longitudinal lung function decline

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Occupational inhalant exposures and longitudinal lung function decline

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Introduction

Lung function peaks in the twenties, and naturally declines with increasing age hereafter [1]. Tobacco smoking is the most important risk factor for accelerated lung function decline, which may lead to chronic obstructive pulmonary disease (COPD) [2]. In addition to smoking, occupational airborne exposures have been associated with lung function decline and COPD [3, 4]. The population attributable fraction of COPD due to occupational exposure has been estimated to be 15-20% [5]. Prior studies have mostly focused on high risk occupations such as coal mining [6, 7], welding [8, 9] and wood processing [10, 11]. Studies examining the association between ongoing exposure and change in lung function in the general population are few and inconclusive [12-20]. A recent study based on data from the Framingham Heart Study found an excess decline in forced expiratory volume in the first second (FEV_1) of 4.5 mL/year in "more likely dust exposed" individuals [14]. Another study based on two general population studies reported an excess decline of 0.6-0.8 mL/year for low and 2-3 mL/year for high exposure of biological and mineral dusts and metals [20]. A third study showed no excess decline in workers exposed to vapours, gases, dusts, and fumes, unless concomitant exposure to pesticides was present [12]. Discrepancies between the estimated impact of occupational airborne exposures and actual findings call for further exploration.

Accounting for occupational exposure in the period between two lung function measurements as an indication of ongoing rather than delayed health effects like tobacco smoking may be crucial [21, 22]. However, prior general population studies on occupational exposure and lung function decline have relied on a single or a few selected jobs held during follow-up [12-15], occupation at study entry [16, 17], or self-reported exposure either at baseline [18] or at the final examination [19].

In the present study, we investigated the association between occupational airborne exposure and longitudinal change in lung function, expressed as annual decline in FEV_1 in two population-based cohort studies from Denmark.

Methods

Study design

Individuals were recruited from two large Danish prospective population-based cohorts [23-25]: the Copenhagen City Heart Study and the Copenhagen General Population Study. The Copenhagen City Heart Study was initiated in 1976 and enrolled 19,825 individuals with subsequent follow-up examinations in 1981–83, 2001–03, and 2011–15. The Copenhagen General Population Study was initiated in 2003, is ongoing, and 109,538 individuals were included in this study. A follow-up examination was initiated from 2014, which at the time of present analyses included 29,884 participants [26]. Individuals in both cohorts were aged 20 years or older. All participants completed a questionnaire and a physical health examination including spirometry at each visit.

We included individuals with lung function measurements at two or more time points (supplementary figure 1). To examine a working population in an age group where lung function is thought to decline in a linear fashion [27], we excluded participants younger than 35 years of age at first lung function measurement and older than 65 at follow-up. Individuals with no employment in the follow-up period or with missing information on smoking habits or education were also excluded. None of the participants appeared in more than one of the cohorts. The cohort studies were approved by the Danish Ethical Committees and were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Lung function

Pre-bronchodilator FEV_1 and forced vital capacity (FVC) were measured in a standing position and repeated at least three times at each study visit under strict instructions from a trained healthcare professional. The test was accepted when the visual appearance of the spirometry tracing was within acceptable range, and

at least two tests from a single visit did not differ more than 5%. The highest values of FEV_1 and FVC were recorded. Three spirometers were used in the Copenhagen City Heart Study: Monaghan M-403 Spirometer (Monaghan, Littleton, Colorado, USA) from 1976-83, Vitalograph Spirometer (Maids Moreton, Buckinghamshire, UK) from 1991-03, and EasyOne Spirometer (ndd Medical Technologies, Zurich, Switzerland) from 2011-2015. In the Copenhagen General Population Study, Vitalograph Spirometer was used in the first 14,625 participants from 2003-05, and EasyOne Spirometer in the remaining participants from 2005-15. Spirometers were replaced when they stopped functioning, and thereby a direct comparison was not possible; however, measurements from the Vitalograph and the EasyOne Spirometers have previously been compared with no major systematic differences of importance to the present study [28, 29]. As recommended by the manufacturers, the Monaghan and the Vitalograph were calibrated daily with a 1-L syringe, and the EasyOne Spirometer was verified regularly with a 3-L syringe.

Occupational exposure

Data on occupational airborne exposure was obtained through several steps. Every Danish citizen has a unique identification number since birth or immigration (the Civil Registration number) recorded in the national Danish Civil Registration System. The national Danish Civil Registration System was combined with the Danish Occupational Cohort (DOC*X) [30] to obtain complete job histories during the follow-up periods. Data included annual employment status (employed/not employed) and job codes according to the Danish version of the International Standard Classification of Occupation (DISCO-88). When a job code was missing, information from the most recent year was imputed (corresponding to 7% of all person-years). The Airborne Chemical Job Exposure Matrix (ACE JEM) [31] assigned occupational airborne exposure to each job code based on expert judgement. ACE JEM was developed for the UK SOC 2000 classification and was converted to DISCO-88 codes. A total of 10 major and 27 sub-major group codes in the DISCO-88 lacked direct translation to SOC 2000 codes. We assigned exposure values by grouping the DISCO-88 codes on a

higher level while taking the population distribution on the contributing DISCO-88-unit groups into account.. The following main categories of airborne agents were considered: mineral dust, biological dust, gases & fumes, and the composite category vapours, gases, dusts, or fumes (VGDF). The ACE JEM dichotomized exposure into exposed and unexposed with additional information on level of exposure: not exposed, low (5-19 % of UK workplace limit), medium (20-49 % of UK workplace limit) and high exposure (≥50 % of UK workplace limit) as well as proportion of exposed individuals (<5%, 5-19%, 20-49%, and 50-100%). Levels of exposure was based on expert judgement of occupational exposure levels which used the UK workplace exposure limit values as benchmarks. No measurements were included in the JEM [31]. We constructed an indexed measure of exposure for each job by multiplying levels of exposure and proportion of exposed workers (supplementary table s1). Exposure was expressed ranging from 0 units (unexposed) to 2.5 units (a level of ≥50 % of the UK workplace limit and more than 50% of all workers exposed) (supplementary table s2). As the ACE JEM only reflected working conditions in the UK from 2000-2013 with no time-axis, we conducted separate analyses for the first years of the Copenhagen City Heart Study from 1976-1990.

Statistical analysis

We studied the association between occupational airborne exposure and change in FEV_1 using linear mixed-effects models with unstructured covariance [32]. In main analyses, the proportion of exposed years during follow-up was calculated by dividing the number of exposed years during a follow-up period by the total number of years. In subsequent analyses, mean units of indexed exposure per year was estimated by summing the units of exposure values for each year of follow-up divided by the total number of years. The outcome was expressed as mean annual change in FEV_1 and calculated for each follow-up period as the difference between the latter and the first of two sequential lung function measurements divided by number of years separating them. A fixed set of a priory explanatory variables were selected, that is, sex,

baseline height (cm), weight (kg), smoking (mean annual pack-years in the follow-up period), educational level (elementary, high school, and academic), and baseline FEV_1 (L). We assumed that FEV_1 decline in the included age group was linear and therefore did not adjust for age in main analyses but carried out sensitivity analyses including age in one model, and age and age^2 in another model. Interaction of occupational exposure on smoking (mean pack-years) and sex was investigated. Each cohort was analyzed separately.

Supplementary analyses included males only, never-smokers only, excluding baseline FEV_1 and annual percentage change in FEV_1/FVC as an alternative outcome. An analysis of co-exposure was conducted. To indicate whether the association between occupational exposure on lung function change varied over time, a secondary analysis was performed with data from the first two rounds of the Copenhagen City Heart Study (1976–78 and 1981–83) as opposed to later years (2001-2015). Excluded participants from the Copenhagen City Heart Study and the Copenhagen General Population Study aged 35-65 years were characterized. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, USA).

Results

In total, 16,144 individuals were included (supplementary figure 1). Mean age at study inclusion was 48 years, and 61% in the Copenhagen City Heart Study were smokers at baseline as opposed to 20% in the Copenhagen General Population Study. Other characteristics are summarized in table 1 and supplementary table S3. Follow-up time ranged from 3 to 27 years with a mean of 9 years. All participants from the Copenhagen General Population Study and the majority from the Copenhagen City Heart Study contributed with a baseline and a single follow-up visit, while 563 contributed with three lung function measurements. DISCO-88 codes were complete with all four digits in 66% of all employed years, whereas 4%, 1%, and 29% were only available at first, second and third level, respectively.

Table 1. Baseline characteristics according to cohort

	CCHS (n=8,202)	CGPS (n=7,942)	Total (n=16,144)
Age in years, mean (SD)	48 (7)	47 (5)	48 (6)
Male, n (%)	3,763 (46)	3,231 (41)	6,994 (43)
Smoking history, n (%)			
Never	1,711 (21)	3,554 (45)	5,265 (33)
Former	1,509 (18)	2,765 (35)	4,274 (26)
Current	4,982 (61)	1,623 (20)	6,605 (41)
Education, n (%)			
Academic	543 (7)	1,939 (24)	2,485 (15)
High school	2,629 (32)	5,268 (66)	7,897 (49)
Elementary	5,027 (61)	735 (9)	5,762 (36)
Height in cm, mean (SD)	169 (9)	173 (9)	171 (9)
Weight in kg, mean (SD)	72 (14)	76 (15)	74 (15)
FEV_1, in L, mean (SD)	2.9 (0.8)	3.3 (0.8)	3.1 (0.8)
FEV_1 %, mean (SD)	87 (16)	96 (13)	91 (16)
FEV_1/FVC, mean (SD)	0.80 (0.10)	0.80 (0.10)	0.80 (0.10)

Abbreviations: CCHS = the Copenhagen City Heart Study. CGPS = the Copenhagen General Population Study. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. FEV_1 % = FEV_1 % of predicted value based on Danish reference values [33].

Table 2 shows the distribution of follow-up years according to type of exposure during different time periods. The proportion of exposed years was relatively constant in all exposure categories. The CGPS contributed with 86 % of follow-up years from the year 2000. Overall results are presented in table 3, and the fully adjusted model in supplementary table s4. Mineral dust, biological dust, gases & fumes, and VGDF were not associated with change in FEV_1. In contrast, smoking one pack-year/year (corresponding to 20 cigarettes a day) was associated with change in FEV_1 of -17 mL/year (95% confidence interval [CI]: -19;-15) (table s3). In addition, baseline FEV_1 as well as female sex were significantly associated with change in FEV_1.

Table 2. Distribution of follow-up years according to occupational airborne exposure and calendar period

	< 1980 years (%)	**1980-1989** years (%)	**1990-1999** years (%)	**≥ 2000** years (%)
Vapours, gases, dusts, or fumes				
No exposure	14,489 (64)	18,684 (71)	6,818 (76)	73,321 (70)
Exposure	8,097 (36)	5,578(29)	2,152 (24)	31,304 (30)
Mineral dust				
No exposure	17,850 (79)	21,932 (83)	7,647 (85)	84,270 (81)
Exposure	4,736 (21)	4,530 (17)	1,323 (15)	20,355 (20)
Biological dust				
No exposure	20,855 (92)	24,616 (93)	8,315 (93)	90,241 (86)
Exposure	1,731 (8)	1,846 (7)	655 (7)	14,384 (14)
Gases & fumes				
No exposure	20,426 (90)	23,835 (90)	8,259 (92)	97,308 (93)
Exposure	2,160 (10)	2,627 (10)	711(8)	7,317 (7)

Years of unemployment not included in the number of follow-up years

Table 3. Mixed model of change in FEV_1 per dichotomized exposed year

	Change in FEV_1, mL/year (95% CI)			
	Copenhagen City Heart Study 1976-2013		**Copenhagen General Population Study 2003-2015**	
	Crude*	Adjusted**	Crude*	Adjusted**
Vapours, gases, dusts, or fumes	-2.9 (-6.4;0.6)	-2,0 (-5.3;1.3)	0.1 (-1.6;1.8)	0.7 (-0.9;2.3)
Mineral dusts	-3.8 (-8.0;0.4)	-2.1 (-6.0;1.8)	0.1 (-1.8;2.1)	0.8 (-1.0;2.7)
Biological dusts	3.7 (-2.2;9.5)	2.8 (-2.7;8.3)	0.1 (-2.1:2.3)	0.5 (-1.7;2.6)
Gases & fumes	-7.6 (-14.0;1.7)	-5.3 (-10.9;0.2)	1.3 (-1.8;4.5)	1.1 (-2.0;4.1)

A negative estimate denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Estimates adjusted for *sex and height **sex, height, weight, smoking (pack-years) per of follow-up year, baseline FEV_1, and education.

In analyses exploring differences between the two included cohorts and time periods using the indexed exposure measure, gases & fumes were associated with a change in FEV_1 of -5.8 mL/year (95% CI: -10.8;-2.3) per exposed unit in the Copenhagen City Heart Study, but not in the Copenhagen General Population Study (table 4). Entering exposure to mineral dusts, biological dusts and gases & fumes in the same model did not change the results , and indexed exposure to gases & fumes in CCHS remained significantly associated with FEV_1 decline (results not shown). In stratified analyses, the association was only seen in early years of the study period (1976-1990) and not in later years. No associations were observed between

mean dichotomized or indexed exposure and % FEV_1/FVC per year (supplementary tables S5 and S6). Analyses restricted to men or never-smokers or including age as well as age^2 or excluding baseline FEV_1 or education as covariates did not change our results. We found no interactions between occupational exposure and smoking or sex.

Table 4. Mixed model of change in FEV_1 per indexed exposed year

	Change in FEV_1, mL/ unit/year (95% CI)			
	Copenhagen City Heart Study		**Copenhagen General Population Study**	
	Crude*	Adjusted**	Crude*	Adjusted**
Vapours, gases, dusts, or fumes	-1.0 (-4.2;2.2)	-0.3 (-3.2;2.8)	0.5 (-1.1;2.0)	0.7 (-0.8;2.3)
Mineral dusts	-1.4 (-5.2;2.3)	-0.4 (-4.0;3.0)	0.2 (1.6;1.9)	0.4 (-1.3;2.1)
Biological dusts	1.7 (-9.6;12.9)	3.5 (-7.0;13.9)	1.1 (-3.3;5.5)	1.2 (-2.9;5.5)
Gases & fumes	**-5.6 (-11.0;-0.3)**	**-5.8 (-10.8;-2.3)**	0.7 (-2.4;3.8)	0.7 (-2.2;3.8)

A negative coefficient denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Unit range: 0 - 2.5 per year. Estimates adjusted for *sex and height **sex, height, weight, pack years per of follow-up year, baseline FEV_1 and education.

Discussion

In two longitudinal population-based cohort studies including 16,144 participants, we found that occupational exposure in the follow-up period to mineral dust, biological dust, gases & fumes, and VGDF were not associated with accelerated lung function decline from 2003-2015. However, exposure to gases & fumes four decades ago was associated with an excess annual FEV_1 decline.

Previous longitudinal general population studies of lung function decline are highly heterogenic and show small associations with airborne occupational agents [12, 14, 18, 20], a greater decline with exposure to an increasing number of agents [19], or no associations at all [13]. The studies rely mostly on self-reported job history or exposures obtained once, assess exposure differently, or differ in study populations which may explain the discrepancies. The most recent longitudinal general population study with similar exposure assessment, ages of participants and a long follow-up, concluded that one year of low exposure to mineral

dust, biological dust, or metals was associated with 0.6-0.7 mL lower FEV_1, and one year of high exposure with 2-3 mL lower FEV_1 [20]. Nine other categories of exposure, including gases & fumes and VGDF were not associated with lower FEV_1. The participants were selected from 38 out of 55 sites located in 23 countries, possibly with different working conditions than in Denmark. Importantly, the study reported that 25 pack-years of smoking were associated with a statistically insignificant decrease in FEV_1 of 11 mL corresponding to 0.4 mL per pack-year. This is inconsistent with both our findings and previous studies showing a mean difference of height-adjusted FEV_1 of 300-400 mL following 25 pack-years [34] or a decrease in FEV_1 of 6-11 mL per pack-year [35, 36]. In addition to pack-years, female sex and baseline FEV_1 were associated with decline in FEV_1, as indicated in previous studies [1, 37].

A meta-analysis based on five longitudinal studies from 1987 to 2003 on occupational exposure to mineral dust found an excess decline in FEV_1 of 1.6 mL per 1 unit ($mg \cdot m^{-3} \cdot years$) of respirable mineral dust [38]. The most prevalent high mineral dust exposed job in our population was construction workers. The geometric mean of respirable dust among indoor demolition workers in Denmark from 2012-2014 has been measured to 1 mg/m^3[39]. A theoretical excess decline in FEV_1 of 1-2 mL per year in exposed individuals would be difficult to demonstrate in our study setup, and the clinical relevance may be questionable.

Ambient air pollution is another type of inhalant hazard which has been associated with lung disease, including accelerated decline in lung function [40] with substantial variability in risk estimates depending upon the sources of air pollution and duration of exposure. Of note, a recent multicenter cohort study and meta-analysis found no associations between FEV_1 decline and ambient air pollution [41].

Our study had several strengths. Job history was quite accurate within the follow-up periods, and we calculated average exposure during follow-up equivalent to cumulative exposure during follow-up, as length of follow-up periods were Indirectly factored into the analyses. Other strengths were repeated lung function measurements and the long follow-up time minimizing the within-person variation of FEV_1 [2].

Other general population-based studies with repeated lung function measurements have mostly relied on self-reported exposure or job history [12-16, 18, 19, 42] with risk of misclassification due to recall bias. Small effects caused by past exposures may be difficult to show. Some industry-based studies might be confounded by the healthy-worker effect, if individuals suffering from problems caused by or associated with the job, quit and are more likely to be lost to follow-up. In our cohort, job change did not directly affect participation.

Occupational history was based on data from the DOC*X database, and we carried prior occupation forward in years of employment, where job titles were missing with the risk of misclassification. Exposure was estimated based upon JEM. This approach has strengths as well as some limitations. The JEM was based upon expert judgements by experienced occupational exposure assessors, but rigorous validation studies using workplace measurements as gold standard are not available. JEM tends to reduce degree of recall bias and hence differential misclassification as opposed to self-reported exposure. However, since JEM may not capture how exposure varies between workers within the same occupation, it may lead to non-differential misclassification. The ACE JEM relied on UK threshold which might differ from the Danish occupational exposure limits. The European Union releases both indicative and mandatory occupational exposure limits [43]. A recent report found strong similarities between systems for setting and achieving compliance with occupational exposure limits in the EU [44]. The major players in setting limits at the level of the EU were reported to be the larger northern European countries, the Nordic countries and the Netherlands. Although a comparative study of the actual values is to our knowledge not available, the differences between the countries are believed to be minor.

We only included participants with two or more lung function measurements, and ideally a higher number of follow-up examinations and measurements would have been preferable. Positive selection, i.e. that healthier subjects choose the most exposed jobs, has previously been shown [17]. Excluded subjects from the Copenhagen City Heart Study and the Copenhagen General Population Study of the same age group as

participants did however not differ significantly regarding exposure (results not shown). We did not exclude participants with lung disorders at baseline, as this could worsen the selection bias towards healthier individuals. The use of different spirometers was a limitation, which is a consequence of the fact that the studies spanned over several decades and reflects the development in the field. Fortunately, exposed and unexposed participants were affected equally due to random sampling.

We studied the association of ongoing occupational exposure on decline in FEV_1 and disregarded prior exposure. It is possible that the effect of airborne exposure is time-dependent: either more harmful at the beginning or following many years of exposure. The response could also be delayed. We were not able to address this in our study. Although studies of the time effect of specific exposures on lung function are emerging [10], much is still unknown. However, if the effects of occupational exposure on FEV_1 resemble cigarette smoking, we would expect that the primary effect occurs concurrently with exposure. The degree of synergy between tobacco and occupational inhalant exposures and lung function decline is complex and could not be accounted for with the present study design. Yet, no interaction between smoking and occupational inhalant exposures were found in associations to FEV_1 decline. We did not have data on cumulative exposure before baseline, and we lacked power to take within subject variation in exposure into consideration. However, jobs were highly robust, with only a few participants changing exposure status during follow-up.

As our study population was limited to European whites, aged 35 to 65 years old in an urban setting, our results cannot be generalized to other groups without caution. We used educational level as a proxy for socioeconomic status. As background and upbringing (i.e. passive smoking, living conditions, medical treatment of diseases) vary across social classes, there is a risk of residual confounding. Furthermore, jobs with exposure to airborne agents are primarily held by people with a lower socioeconomic background, which may confound the results. Characteristics of participants from the Copenhagen City Heart Study and the Copenhagen General Population Study differed greatly regarding smoking habits and educational levels

and reflect the overall development in Denmark, as in most Western societies. Consequently, direct comparison of results from the two cohorts cannot be made without caution. We adjusted for education and smoking habits to mitigate bias due to cohort differences and to enhance comparability. Estimates from crude and adjusted analyses in both cohorts were largely similar, thereby suggesting less influence of residual confounding. Pesticide exposure may be associated with lung function decline but was only classified in a broader category of mists in the ACE JEM. Study participants were inhabitants of Copenhagen (the capital of Denmark) and exposure to pesticides was believed to be rare.

Our results suggest that none of the selected airborne occupational exposures are currently associated with an excess decline in FEV_1 and consequently do not lead to an increased risk of developing COPD. However, exposure to gases & fumes was associated with decline in FEV_1 in the early study period. This is plausible as most airborne occupational exposures in high income countries including Denmark have declined substantially since the 1970ies [45], and the access to and use of respiratory protective equipment has increased . JEM assigned exposure to gases & fumes is highly correlated with exposure to mineral dust, and in 81% of all gases & fumes exposed years, exposure to mineral dust was also present. Our study relied on cumulative exposure during follow-up, and interaction analyses based on ever- versus never-exposure or groups of exposure did not seem appropriate. Co-exposure analyses did not change the main results. The lack of extensive interaction analyses is a limitation to our study design as results are most likely carried by a joint effect.

In conclusion, we found no associations between exposure to mineral dust, biological dust or gases & fumes and accelerated lung function decline in recent years.

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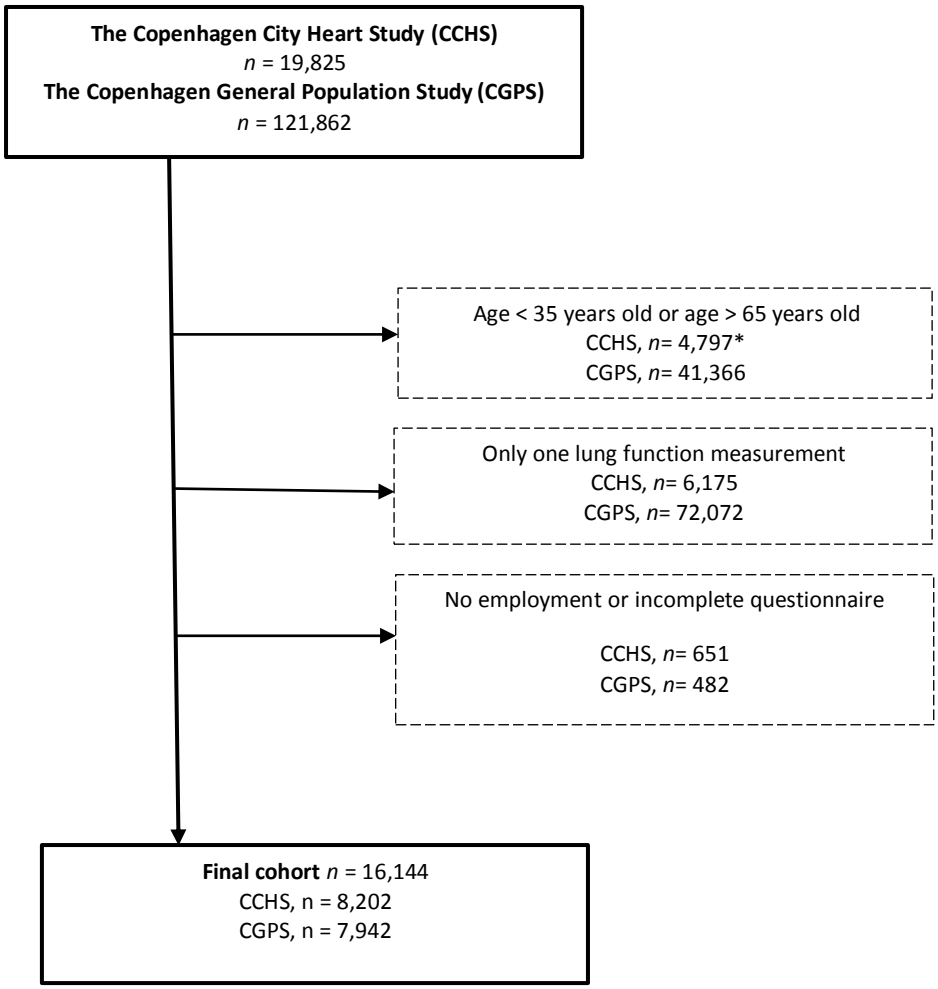
Supplementary Data



Supplementary Figure 1

Flowchart of the study population with at least two lung function measurements, aged 35-65 years old at baseline and follow-ups, *study visits in CCHS from 1991-1994 excluded **employed for at least one year during follow-up, with complete questionnaire data regarding smoking parameters and education.

Table S1. Principles for assigned values to the Airborne Chemical Job Exposure Matrix

	Category	Mean %	Assigned value
Level	Not exposed	0%	0
	Low (5-19 % of UK workplace limit)	12%	0.2
	Medium (20-49 % of UK workplace limit)	35%	0.5
	High (≥50 % of UK workplace limit)	75%	1
Proportion	0%	0%	0
	1-9%	5%	0.2
	10-50%	30%	1
	51-100%	75%	2.5

Table S2. Indexed exposure in the study population according to main category of exposure

		0 units	0.04-0.5 units	1-2 units	2.5 unit
CCHS	Vapours, gases, dusts or fumes	70%	23%	5%	3%
	Mineral dust	82%	12%	4%	2%
	Biological dust	91%	7%	1%	0%
	Gases & fumes	91%	5%	3%	1%
CGPS	Vapours, gases, dusts or fumes	70%	24%	3%	3%
	Mineral dust	80%	15%	2%	3%
	Biological dust	86%	12%	2%	0%
	Gases & fumes	93%	4%	3%	0%

Abbreviations: CCHS: The Copenhagen City Heart Study; CGPS: The Copenhagen City General Population Study. Numbers do not sum up to 100% due to rounding error.

Table 1. Baseline characteristics according to cohort

	CCHS (n=8,202)	CGPS (n=7,942)	Total (n=16,144)
Age in years, mean (SD)	48 (7)	47 (5)	48 (6)
Male, n (%)	3,763 (46)	3,231 (41)	6,994 (43)
Smoking history, n (%)			
Never	1,711 (21)	3,554 (45)	5,265 (33)
Former	1,509 (18)	2,765 (35)	4,274 (26)
Current	4,982 (61)	1,623 (20)	6,605 (41)
Education, n (%)			
Academic	543 (7)	1,939 (24)	2,485 (15)
High school	2,629 (32)	5,268 (66)	7,897 (49)
Elementary	5,027 (61)	735 (9)	5,762 (36)
Height in cm, mean (SD)	169 (9)	173 (9)	171 (9)
Weight in kg, mean (SD)	72 (14)	76 (15)	74 (15)
FEV_1, in L, mean (SD)	2.9 (0.8)	3.3 (0.8)	3.1 (0.8)
FEV_1 %, mean (SD)	87 (16)	96 (13)	91 (16)
FEV_1/FVC, mean (SD)	0.80 (0.10)	0.80 (0.10)	0.80 (0.10)

Abbreviations: CCHS = the Copenhagen City Heart Study. CGPS = the Copenhagen General Population Study. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. FEV_1 % = FEV_1 % of predicted value based on Danish reference values.

Table S4. Change in FEV_1 per year in the fully adjusted model in The Copenhagen General Population Study

	Change in FEV_1 mL/year (95% CI)
Intercept	-12 (-30;7)
Vapours, gases, dusts or fumes (per exposed year)	0.7 (-0.9;2.3)
Female sex	-13 (-15;-11)
Smoking (pack-year/ year)	-17 (-19;-15)
Baseline FEV_1 (L)	-15 (-17;-14)
Education	
Elementary (ref)	Reference
High school	0.4 (-1.7;3.2)
Academic	0.7 (-1.7;2.7)
Height (cm)	0.3 (0.2;0.4)
Weight (kg)	0.01 (-0.04; 0.07)

A negative coefficient denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Abbreviations: FEV_1: forced expiratory volume in one second.

Table S5. Mixed model of FEV_1/FVC % change per year of dichotomized exposure

	Change in FEV_1/FVC % per year (95% CI)	
	The Copenhagen City Heart Study	The Copenhagen General Population Study
Vapors, gases, dusts and fumes	-0.1 (0.6;0.5)	-0.1 (-0,4;0.2)
Mineral dusts	-0.1 (-0.8;0.5)	0.01 (-0.3;0-3)
Biological dusts	-0.4 (-1.3;0.6)	-0.1 (-0.5;0.3)
Gases & fumes	0.5 (-0.5;1.4)	0.4 (-0.2;0.9)

A negative coefficient denotes a more rapid decline in FEV_1/FVC %; a positive coefficient a less rapid decline
Abbreviations: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Estimates adjusted for weight, height, sex, pack years per of follow-up year, baseline FEV_1 and education.

Table S6. Mixed model of FEV1/FVC % change per exposed year in indexed exposure

	Change in FEV_1/FVC % per year (95% CI)	
	The Copenhagen City Heart Study	The Copenhagen General Population Study
Vapors, gases, dusts and fumes	0.1 (-0.5;0.6)	0.1 (-0.2;0.3)
Mineral dusts	0.004 (-0.6;0.6)	0.2 (-0.1;0.5)
Biological dusts	0.8 (-1.0;2.6)	0.3 (-0.5;1.0)
Gases & fumes	0.4 (-0.5;1.2)	0.4 (-0.1;1.0)

A negative coefficient denotes a more rapid decline in FEV_1/FVC %; a positive coefficient a less rapid decline.
Abbreviations: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Estimates adjusted for weight, height, sex, pack years per of follow-up year, baseline FEV_1 and education.

Table S7. Correlation table between indexed exposure measures according to cohort

		Gases & fumes	Biological dust
CCHS	**Mineral dust**	0.56 (p<0.0001)	0.39 (p<0.0001)
	Biological dust	0.25 (p<0.0001)	
CGPS	**Mineral dust**	0.60 (p<0.0001)	0.50 (p<0.0001)
	Biological dust	0.33 (p<0.0001)	

Correlations presented as spearman rank correlation coefficient. Abbreviations: CCHS = the Copenhagen City Heart Study. CGPS = the Copenhagen General Population Study.

Occupational exposure and chronic airway disease

PhD Thesis

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Preface

The thesis was carried out at the Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg Hospital from 2018 to 2020. Studies were performed in collaboration with Occupational and Environmental Medicine at the University of Birmingham. The thesis was financially supported by grants from The Danish Working Environment Research Fund (grant number 40-2016-09 20165103813) and The Research Committee at Bispebjerg and Frederiksberg Hospital.

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List of papers

Paper I

Chronic productive cough and inhalant occupational exposure – a study of the general population. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Nordestgaard BG, Sadhra S, Kurmi O and Bonde JPE*. International Archives of Occupational and Environmental Health*, 2021, 1-8.

Paper II

Occupational inhalant exposures and longitudinal lung function decline. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Çolak Y, Afzal S, Nordestgaard BG, Sadhra S, Kurmi O and Bonde JPE. Manuscript (In revision, European Respiratory Journal, submitted November 2020).

Paper III

Occupational exposures and exacerbations of asthma and COPD-A general population study. Skaaby S, Flachs EM, Lange P, Schlünssen V, Marott JL, Brauer C, Nordestgaard BG, Sadhra S, Kurmi O, Bonde JPE. *Plos one*, 2020, 15.12: e0243826.

Summary

Introduction

Asthma, chronic obstructive pulmonary disease (COPD) and chronic productive cough are highly prevalent worldwide. The three lung conditions might be caused or worsened by airborne hazards at work, and an estimated 10–20% are believed to be attributable to occupational inhalant exposures. Airborne occupational exposure levels have, however, generally declined during the past decades, and recent findings question the associations. Our aims were to study the association between past and present occupational airborne exposures and lung function decline, chronic productive cough and exacerbations of asthma and COPD.

Methods

The study was based on two general population-based cohorts; the Copenhagen City Heart Study and the Copenhagen General Population Study. Information on jobs held during follow-up, smoking habits, educational level, height, weight, spirometry, chronic productive cough, self-reported asthma, prescriptions for oral corticosteroids, emergency care unit assessments and hospital admissions were derived from registers, questionnaires, and physical examinations. Occupational exposure to mineral dusts, biological dusts, gases and fumes, a composite variable (vapours, gases, dusts, or fumes; VGDF) as well as high molecular weight sensitizers, low molecular weight sensitizers and irritants were assigned by job exposure matrices. Statistical analyses included mixed effects models, generalized estimating equations and Cox regression.

Results

Selected airborne occupational exposures from 2003 to 2017 were not associated with FEV_1 decline, exacerbations of asthma and COPD or chronic productive cough in non-smokers. High levels of all selected exposures in smokers were associated with chronic productive cough with odds ratios ranging from 1.2 (95% confidence interval, CI 1.0;1.4) to 1.5 (95% CI 1.1;2.0).

In analyses including exposures before 1990, dichotomized exposure and FEV_1 decline were not significantly associated. An indexed measure of gases & fumes was associated with an accelerated decline of FEV_1 of 6 mL/unit/year (95% confidence interval: 2;11) during 1976–1990. Chronic productive cough was in smokers associated with exposure to high levels of mineral dust, biological dust, gases & fumes and VGDF, and in non-smokers with high levels of VGDF and low levels of mineral dust during 1976–1983, odds ratios ranging from 1.3 (95% CI 1.1;1.6) to 1.7 (95% CI 1.1;2.4).

Conclusion

In our study, occupational airborne exposures were not significantly associated with lung function decline, or exacerbations in asthma and COPD in recent years in two, large Danish cohorts from the general population. Chronic productive cough was associated with selected occupational exposures in smokers only during the time period from 2003–2017, whereas significant associations were seen also in non-smokers in years before 1990. Exposure to gases & fumes was associated with lung function decline in years before 1990.

Our results suggest that selected occupational airborne exposures might have accelerated lung function decline decades ago but not in the recent years. Further studies with quantitative exposure assignment and with participants serving as their own controls are warranted.

Dansk resumé

Introduktion

Astma, kronisk obstruktiv lungesygdom (KOL) og kronisk, produktiv hoste forekommer hyppigt globalt. De tre lungesygdomme kan skyldes eller forværres af luftbårne stoffer på arbejdet, og det anslås, at 10–20% skyldes erhvervsmæssig eksponering. Omfanget af erhvervsmæssig, luftbåren eksponering er dog faldet de seneste årtier, og nyere undersøgelser anfægter de påviste sammenhænge. Vores formål var at undersøge sammenhængen mellem erhvervsmæssig eksponering og nedsat lungefunktion, kronisk produktiv hoste samt forværring af astma og KOL.

Metoder

Undersøgelsen baserer sig på to befolkningsundersøgelser; Østerbroundersøgelsen og Herlev Østerbroundersøgelsen. Oplysning om jobtitel, rygning, uddannelsesniveau, højde, vægt, spirometri, kronisk produktiv hoste, astma, recepter på perorale kortikosteroider, skadestuebesøg og hospitalsindlæggelser var samlet i registre, spørgeskemaer samt ved klinisk undersøgelse. Jobeksponeringsmatricer blev anvendt til at tildele erhvervsmæssig udsættelse for mineralsk støv, biologisk støv, gasser og dampe, en sammensat variabel bestående af dampe, gasser, støv eller røg (VGDF) samt højmolekylære stoffer, lavmolekylære stoffer og irritanter i hvert job. Sammenhænge blev undersøgt vha. mixed effects models, generalized estimating equations og Cox-regression.

Resultater

Erhvervsmæssige eksponering var fra 2003 til 2017 ikke associeret med fald i FEV_1, forværring af astma og KOL eller kronisk, produktiv hoste blandt ikke-rygere. Høje niveauer af alle eksponeringskategorier var associeret med kronisk produktiv hoste blandt rygere med odds-ratioer fra 1,2 (95% konfidensinterval, CI 1,0; 1,4) til 1,5 (95% CI 1,1; 2,0).

Fald i FEV_1, var i perioden 1976 til 1990 ikke signifikant associeret med dikotomiseret erhvervsmæssig eksponering, mens indekseret eksponering for gasser og dampe var associeret med et fald i FEV_1 på 6 ml/ enhed/ år (95% konfidensinterval: 2;11). Kronisk produktiv hoste var i perioden 1976 til 1983 blandt rygere associeret med eksponering for høje niveauer af mineralsk støv, biologisk støv, gasser og dampe og VGDF, og blandt ikke-rygere associeret med høje niveauer af VGDF og lave niveauer af mineralsk støv med odds ratioer mellem 1,3 (95% CI 1,1; 1,6) og 1,7 (95% CI 1,1; 2,4).

Konklusion

Erhvervsmæssig, luftbåren eksponering var i vores undersøgelse ikke signifikant associeret med lungefunktionsfald eller forværring af astma og KOL fra 2003 til 2017 i to store, danske befolkningsundersøgelser. Signifikant association til kronisk, produktiv hoste fandtes kun blandt rygere i de senere år, mens der også var signifikante sammenhænge blandt ikke-rygere i år før 1990. Indekseret eksponering for gasser og dampe var associeret med fald i lungefunktion før 1990.

Vores resultater typer på, at udvalgte, erhvervsmæssige eksponeringer har været associeret med fald i lungefunktion tidligere, men ikke aktuelt. Der er behov for yderligere undersøgelser med kvantitative eksponeringsmål, og hvor hver deltager fungerer som sin egen kontrol.

Introduction

Chronic bronchitis, asthma and chronic obstructive pulmonary disease (COPD) are prevalent diseases in the general population with large, international differences [1, 2]. Globally, more than 300 million people suffer from asthma, and 250 million from COPD, and the prevalence of both diseases is still increasing [3, 4]. The proportion of people in Denmark affected by COPD is among the highest worldwide [5-8].

Asthma and COPD are chronic diseases. Lung function changes in COPD are most commonly progressive, and chronic inflammation in asthma persistent, despite variable symptoms [4, 9]. Chronic pulmonary symptoms such as chronic productive cough might precede airflow limitation [10].

Environmental factors are thought to play a major role in disease development. Smoking is the greatest risk factor in COPD and is associated with exacerbations of asthma [4, 9]. An estimated one fourth to one third of COPD patients have, however, never smoked [11], and tobacco smoking is declining globally [12]. Other modifiable risk factors need to be explored, including occupational exposures. The occupational population attributable fractions (PAF) of chronic productive cough, asthma and COPD are globally estimated to be 10-20% [13]. In addition, occupational exposures are suspected to aggravate existing respiratory disease. Established associations are largely based on cross-sectional or industry specific studies, whereas recent prospective, general population studies on lung function decline, chronic productive cough and exacerbations of obstructive lung disease are limited, and results are inconclusive. Differences might be explained by bias and confounding but may also reflect differences in past and present working conditions. Overall declining levels of occupational exposures [14], a greater access to protective equipment and decreasing high exposed trades in developed countries might contribute to inconsistencies. More longitudinal studies of the general population are required to support or challenge established associations.

Background

Occupational airborne exposures

Occupational airborne exposures are potential health hazards in the workplace. Most are invisible and without smell. Inhalant exposures may differ in structure, source and toxicological properties. Main structures include gaseous forms (gases and vapours), and aerosols (dusts and fumes) which are suspensions of liquids or solid particles in air [15] (table 4). Both natural and man-made sources of airborne exposures exist. Classification based on toxicological properties of chemicals is frequently used in occupational asthma.

There is no standardized approach to systematically assess occupational inhalant exposure. Instead, self-reported outcomes (interviews or surveys), workplace observations, expert judgement, measurements, or combined methods such as job exposure matrices are often applied. A job exposure matrix (JEM) assigns exposure characteristics such as type, level, proportion of exposed workers and calendar period to each included job code. Thereby, all workers with the same job title have identical exposure characteristics. JEMs are useful in general population studies, where multiple jobs and industries are present (table 1) [16, 17].

Table 1. Possible advantages and limitations with job exposure matrices

Possible advantages	Possible limitations
Simple	Low sensitivity
Reproducible	Misclassification
Transparent exposure allocation	- Non-differential (Berkson-type error) and differential misclassification
Multiple exposures possible	- No variability within the same job code
Scalable	- Job categories not developed for exposure classification
Inexpensive once developed	Might not be applicable to other regions/countries/time periods
Might reduce reporting and recall bias	

Industry or occupation specific studies, in comparison to general population studies, may provide more detailed exposure characteristics but are vulnerable to the healthy worker effect [18] and may not reflect exposure levels in the general population.

Levels and composition of airborne occupational exposures have changed during the last decades. A review based on measurements of airborne occupational exposures from 1940 to 2003 found overall declining trends in exposure to aerosols, gases and vapours [14]. The study evaluated measurement datasets as well as scientific papers and reports. Improved technology and increasing governmental regulation were believed to

be important contributors. In Denmark, a governmental authority securing worker protection has existed since 1873. In 1977, the Working Environment Act was established to identify health hazards at work and impose the responsibility of safe working conditions at the employer.

Occupational airborne exposures and airway disease

Once inhaled, only a small fraction of airborne hazards is deposited in the lungs. Size of the particle is an important determinant of deposition [19]. Large particles (>2-3 μm diameter) are filtered out by hair in the nostrils or deposit in the upper respiratory tract, whereas smaller particles (< 100 nm diameter) may reach the gas exchange regions [20, 21]. Size-selective deposition is used in occupational medicine to establish threshold limits and is divided into particulate fractions; inhalable fraction (the fraction entering the nose and mouth by breathing), thoracic fraction (the fraction that reaches beyond the larynx), and the respirable fraction (the fraction reaching the gas exchange regions of the lungs) [22]. Generally, aerosols consist of particles of different sizes with few exceptions [23]. Many occupational airborne exposures are believed to resemble cigarette smoking as both are mixtures of aerosols and gases [24].

Airborne hazards are associated with disorders in the lungs such as chronic obstructive pulmonary disease (COPD), asthma, and chronic bronchitis. The conditions are overlapping [25, 26] and share characteristics such as chronic inflammation but differ in etiology and clinical features [4, 27, 28].

Chronic productive cough

Chronic productive cough is in the thesis defined as cough with sputum for at least three months every year and is used synonymously with chronic bronchitis. Risk factors include tobacco smoking, occupational airborne hazards, and rhinosinus disease [29]. Chronic bronchitis is associated with loss of lung function and acute respiratory exacerbations [30, 31], and an estimated 14–74% of all COPD patients suffer from chronic productive cough [28]. Chronic cough in asthma might be productive or non-productive, but presence of chronic productive cough decrease the likelihood of asthma when making the initial diagnosis [4].

Mucus is a part of the defense mechanism in the lungs and covers the airway surface [32]. Inhaled particles might be cleared from the lungs by entrapment in mucus and transported from the distal airways towards the throat by ciliary activity or by cough [32]. Coughing up phlegm is believed to be caused by hypersecretion and decreased elimination of mucus [28]. This may lead to worsening of airway limitation by obstruction of small airways and change in airway surface tension [28].

Associations between chronic bronchitis and occupational exposures have been found in smaller, industry or occupation specific studies with emphasis on high-risk trades such as miners [33, 34], grain [35] and textile workers [36]. In line with this, larger, general population studies have reported composite variables of inhalant exposures to be associated with chronic bronchitis [37-42]. However, in a recent study of 8,794 participants, ever being exposed during follow-up to one of 12 exposure categories was not significantly associated with incident chronic bronchitis [43].

COPD and lung function decline

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and pulmonary symptoms [44]. Several genetic and environmental factors, including lung growth and development, prior respiratory infections, genetic predispositions, chronic bronchitis, asthma and exposure to inhalant hazards are associated with permanent lung function impairment [27, 45]. A major risk factor for COPD is tobacco smoking [9]. Symptoms include cough, dyspnea and/or production of mucus. In addition to symptoms, spirometry is required to establish the diagnosis. A fixed ratio below 0.70 of forced expiratory volume in 1 second (FEV_1) divided by the forced expiratory volume (FVC) after inhalation of a bronchodilator confirms persistent airflow limitation [9]. Both FEV_1 and FVC reach a maximum at the age of approximately 20 years and after a variable plateau phase decline steadily from the age of 30-35 years [46]. Airflow limitation may arise as a result of disturbances in all phases of lung development and aging [47]. In healthy, middle-aged males, the age-related decline in FEV_1 is approximately 30 mL per year and in females approximately 25 mL per year [45]. COPD is in some individuals the clinical endpoint of many years of excess decline in FEV_1 but accelerated decline is not an obligate finding [9]. In a recent study, a more rapid decline was only seen in half of the participants presenting with airflow limitation [48]. In the remaining, the decline was only excess when compared to individuals with a similar, low baseline FEV_1. In healthy individuals, most resistance to airflow is in the proximal airways [49]. In COPD, airway obstruction is mainly due to small airway disease and destruction of the lung parenchyma causing emphysema [9, 27]. Chronic inflammation as well as mucus gland hyperplasia, fewer and more narrow small airways, and airway collapse are characteristics [50, 51]. The mechanisms resulting in decline in lung function are largely unknown. Genetics, immunological response, and disturbance in cellular repair are believed to be of importance [52]. A well-described, genetic risk factor for COPD is alpha-1 antitrypsin deficiency [53]. Smoking is associated with accelerated development of COPD in alpha-1 antitrypsin deficient patients [53], whereas the association with occupational exposures needs further exploration [54].

COPD has been associated with occupational airborne exposures in many cross-sectional studies [55]. Exposure assessment in cross-sectional studies of the general population has widely been based on current or longest-held job or “ever” or “never”

exposure [56-68]. Significant associations have in many studies been limited to different subgroups of participants or to some but not all the selected exposures [56, 59, 61, 64, 66]. In analyses using cumulative exposure measures, associations have been less evident [39, 59, 60, 69]. Below, main conclusions from longitudinal studies and meta-analyses are described.

Original longitudinal studies

Results from longitudinal, general population studies on occupational inhalant exposure and lung function decline are conflicting [38, 70-82]. An overview of longitudinal general population studies with lung function decline and exposure to one or more of the overall categories of exposure examined in the thesis (mineral dust, biological dust, gases & fumes and/or a composite variable) is presented in table 2. The ECRHS cohort participants were a part of two of the studies [38, 71] but as findings differed both are mentioned. Studies which only involved subtypes of exposure such as quarts or welding fumes [76, 82] were not included in the table.

All studies included in table 2 were longitudinal and sampled from the general population but highly heterogeneous, particularly regarding exposure assignment, timing of exposure, and time period.

Longitudinal studies of occupation or industry specific cohorts have shown similar differences regarding lung function decline. No significant associations between decline in FEV_1 and ongoing exposure in steel workers [83], coal miners [84, 85] and bleachery workers [86] have been reported, while significant associations were found in another cohort of coal miners [87], among workers in grain processing and animal feed industry [88], in cotton textile workers [89], subgroups of dairy farmers (85), tunnel workers [90] and wood dust exposed workers [91]

Table 2. Longitudinal general population studies of selected occupational exposures and lung function decline

First author year, country [reference]	Cohort	N	Exposure assessment	Exposure period, outcome period, (mean follow-up)	Measure of association: decline in FEV_1, otherwise stated
Faruque 2020, Netherlands [70]	Lifeline cohort participants	13,759	Self-reported job at baseline, JEM	NA – 2013, 2006 – NA (5)	Current or latest job at baseline: **Biological dust,** high levels: 4 mL/year (95% CI 0;8). Interaction with smoking status (NA). Finding labelled inconsistent. Low levels: NSA. **Mineral dust**, g**ases/fumes**: NSA
Lytras 2020, 23 countries, [71]	ECRHS and SAPALDIA participants	17,833	Self-reported jobs held during follow-up, JEM	1991 – 2012 1991 – 2012 (16)	Cumulative exposure during follow-up: **Mineral dust** and **biological dust:** 0.6-0.7 mL/low exposed year (95% CI NA) ; 2-3 mL/high exposed year (95% CI NA). **Gases/fumes and composite variable**: NSA
Alif 2019, Australia [72]	Tasmanian Longitudinal Health Study	767	Self-reported job history in the 2002-08 follow-up, JEM	~1980 – 2008 2002 – 2012 (5)	Lifetime occupational exposure: **Gases/fumes:** ever vs. never: 11 mL/year (95% CI 3;20). Cumulative exposure: 0.1 mL/ exposure-unit-year (95% CI 0.1;0.3). **Mineral dust, biological dust**: NSA
Tagiyeva 2017, Scotland [73]	WHEASE study participants	237	Self-reported job history at last follow-up, JEM	~1970 – 2014 1989 – 2014 (NA)	Lifetime occupational exposure: **Biological dusts** and **vapours:** ever vs. never: 3 (95% CI 1;6) FEV_1 % predicted. **Mineral dust, gases, fumes:** NSA
Liao 2015, US [74]	Framingham Heart Study, offspring cohort	1,332	Job title at last follow-up, JEM	NA NA (17)	More vs. less likely dust exposed at last follow-up: **Dusts:** 5 mL/year (SE ± 2)
de Jong 2014, Netherlands [75]	Vlagtwedde-Vlaardingen cohort study	2,527	Self-reported job history at last follow-up, JEM	~1955 – 1990 1965 – 1990 (16^{+})	Current or latest job at last follow-up and cumulative exposure in three jobs: **Composite variable:** NSA
Harber 2007, US & Canada [77]	Active smokers with COPD at study entry	5,724	Self-reported exposure at every study visit	1986 – 1991 1986 – 1991 (5)	Exposure at each follow-up: **Dust: NSA** **Fume**: Males: 0.25% predicted reduction in FEV_1 % predicted. Females: NSA
Sunyer 2005, 14 countries [38]	ECRHS participants	6,481	Self-reported job history at last follow-up, JEM	1991 – 2012 1991 – 2002 (9)	Ever high vs. ever low and not high vs. not exposed during follow-up + sensitivity analysis with cumulative exposure during follow-up: **Biological dust, mineral dust, gas, fumes:** NSA
Krzyzanowski 1986, Poland [78]	Random sample of residents in Cracow	1,864	Self-reported exposure at baseline	~ 1920 – 1981 1968 – 1981 (13)	Lifetime occupational exposure ≥ five years at baseline: **Dusts**: Males: 7 mL/year (95% CI NA) . Females: NSA
Kauffmann 1982, France [79]	Male factory workers, no asthma at baseline	556	Expert assigned exposure to workplace at baseline	1960 – (1972) 1960 – 1972 (12)	Exposure at baseline: **Mineral dust, biological dust and gases:** FEV_1 slope (52, 58, 47 mL/year, respectively), significantly different than non-exposed (42 mL/year)

Associations to mineral dust, biological dust, gases, fumes, vapours and/or composite variables listed. $^{+}$ median.
Abbreviations: JEM: job exposure matrix; NA: not available; NSA: not statistically significant; vs: versus

Meta-analyses

A few meta-analyses on occupational exposures and COPD have been conducted. Overall dust exposure was reported to be associated with COPD with an odds ratio of 1.5 (95% CI 1.3;1.8) based on nine studies [92]. COPD was significantly associated with mineral and biological dusts, and gases and fumes with a pooled odds ratio of 1.2 (95% CI 1.2;1.3) in another meta-analysis based on 29 JEM assigned exposure studies [93]. In a third meta-analysis, exposure to low mineral dust and high gases/fumes were the only statistically significant findings with odds ratios of 1.2 (95% CI 1.0;1.3) and 1.2 (95% CI 1.0;1.4), respectively [94].

Meta-analyses on occupational exposures and lung function decline are limited to specific subgroups of exposure. A meta-analysis of 14 studies found that biological dust was associated with an excess decline in FEV_1 of 5 mL/ year (95% CI 0.1; 10) [95]. Another meta-analysis on five studies found welding fumes to be associated with a non-significant excess FEV_1 decline of 9 mL/year (95% CI -5; 23) [96]. Finally, a meta-analysis of 27 studies reported that a cumulative, biopersistent, granular mineral dust concentration of 1 $mg \cdot m^{-3} \cdot$years was associated with FEV_1 decline of 2 mL (95% CI 1;2) [97].

Asthma

Asthma is defined as airflow limitation that primarily normalizes spontaneously or in response to medicine, and variable symptoms such as wheezing, dyspnea, chest tightness, and cough [4]. Asthma is heterogenous with several pheno- and endotypes. The phenotypes share characteristics but differ in clinical and pathological features, whereas the endotypes are defined based on presence and type of airway inflammation [98-100]. Endotypes are broadly divided into type 2 (T2) high and T2-low asthma [100]. Atopic asthma is an example of a T2 high asthma based on allergic sensitization[100]. Work-related asthma is generally characterized as asthma caused by occupational inhalant hazards and asthma exacerbated by workplace exposures.

Airway obstruction in asthma is mainly explained by contraction of bronchial smooth muscle and edema of airway mucosa and sometimes also airway remodeling with persistent narrowing of the airways [101]. The involvement of large airways in asthma is well established, and more recent studies have shown inflammation in small airways as well [102]. Possible triggers of occupational asthma are divided into high and low molecular weight sensitizers and irritants. High molecular weight sensitizers may cause asthma by production of specific IgE antibodies towards the agent [98] whereas mechanisms of asthma induced by low molecular weight sensitizers are poorly understood with only a small fraction caused by specific IgE antibodies [103]. Asthma following accidentally high level of irritants or a longer period of exposure to lower levels of irritants is clinically well-described, but mechanisms are largely unknown [103-106].

Exacerbations of asthma and COPD

Exacerbations of asthma and COPD are acute worsening of symptoms beyond day-to-day variation [4, 107] and share triggers including respiratory viruses and gastroesophageal reflux [108, 109]. Inhalant hazards have been found to be associated with exacerbations of COPD [55] and asthma [4], but mechanisms are not fully understood. Studies of occupational inhalant exposures and exacerbations of asthma and COPD are few with conflicting results [110-112].

Objectives

The objectives were to examine broad categories of occupational airborne exposure and chronic productive cough, lung function decline, and exacerbations of asthma and COPD. The specific aims were to investigate:

1. The association of occupational exposure to mineral dusts, biological dusts and/or gases & fumes and chronic productive cough
2. The association between occupational exposure to mineral dusts, biological dusts and/or gases & fumes and decline in forced expiratory volume in 1 second (FEV_1) in a longitudinal design
3. The association between occupational exposure to mineral dusts, biological dusts and/or gases & fumes, high molecular sensitizers, low molecular sensitizers and irritants and exacerbations of asthma and chronic obstructive pulmonary disease (COPD)

Materials and methods

Study populations

The populations were selected from two, large general population studies conducted in Copenhagen, the capital of Denmark; the Copenhagen City Heart Study and the Copenhagen General Population Study. An overview of the cohorts is found in table 3. Participants from both studies were identified in the Danish Civil Registration System and recruited to reflect the Danish population of Caucasians and Danish descent aged 20-100 years. A questionnaire, a physical examination including spirometry and blood samples were collected at every study visit. The studies were approved by Danish ethical committees, and written informed consent was obtained from all participants.

A random sample of residents of inner Copenhagen, stratified into 5-year age groups were invited from 1976–78 to participate in the Copenhagen City Heart Study. In succeeding rounds of examinations, the entire sample was re-invited, and new subjects from the youngest age groups were included [113]. A total of 109,538 participants randomly selected from the greater Copenhagen area were enrolled in the first round of examinations of the Copenhagen General Population Study from 2003–2014. Individuals living in the same area as the first round of examinations were invited to participate in the second round of examinations, resulting in a combination of newly invited and re-invited subjects [114].

Table 3. Characteristics of the Copenhagen City Heart Study (CCHS) and the General Population Study (CPHS)

Cohort	Round	Years	Participants	Participation rate
CCHS	1	1976–78	14,223	74%
	2	1981–83	12,698	70%
	3	1991–94	10,135	61%
	4	2001–03	6,235	50%
	5	2011–15	4,543	49%
CGPS	1	2003–14	109,939	43%
	2	2014–15	29,884	-

Information on residency, migration and vital status of the participants were identified in The Danish Civil Registration System [115].

Exposure assessment

Exposure was assessed in two steps. Job titles held by the participants in the selected years were retrieved and combined with one or two exposure matrices to assign exposure.
Job codes were provided by the Danish Occupational Cohort*X (DOC*X) [116], a database with information on labour market attachment and job titles year by year on all Danish citizens. A total of 480 different DISCO-88 coded jobs were held by the study population during 1976–2017. Job codes were then linked with the JEM. We chose the following overall categories of exposure: mineral dusts, biological dusts, gases & fumes, and the composite variable vapours, gases, dusts or fumes (VGDF) assigned by the Airborne Chemical Job Exposure Matrix (ACE JEM) [117]. VGDF comprised of vapours, gases, dusts or fumes exposure. The category of gases & fumes included jobs exposed to both gases and fumes. Therefore, job titles with VGDF exposure did not equal the total of mineral dust, biological dust and gases & fumes. Mineral dusts and biological dusts were in the ACE JEM equivalent to inorganic and organic dusts, respectively. In analyses of occupational exposures and exacerbations of asthma and COPD, high molecular weight sensitizers, low molecular weight sensitizers and irritants were additionally included and assigned by the Occupational Asthma-specific JEM (OAsJEM) [118]. An overview of selected categories of occupational airborne exposure is presented in table 4. The categories are overlapping and non-comprehensive.

Table 4. Characteristics of selected occupational exposure categories

Exposure category	Classification based on	Characteristics	Examples	Occupations from study population
Mineral dusts	Source	Aerosols from mineral or metal	Asbestos, cement, aluminum oxide	Construction worker, welder, motor vehicle mechanic
Biological dusts	Source	Aerosols from plants and animals	Flour, wood, pollen	Baker, construction worker, wood processing operator
Gases	Structure	Gaseous state of substance or matter	Carbon monoxide, ammonia, chlorine	Blacksmith, cook, firefighter
Fumes	Structure	Volatilized solid condensed in air	Welding fume, diesel fume, lead fume	
Vapours	Structure	Gaseous state of liquid or solid substance	Benzene, isocyanate, aldehyde	Cleaner, painter, motor vehicle mechanic
High molecular weight sensitizers	Toxicological properties	Plant and animal proteins or polysaccharides, ≥10 kilodaltons	Material from flour, animals and enzymes	Veterinarian, cook, baker
Low molecular weight sensitizers	Toxicological properties	Chemicals and metals < 10 kilodaltons	Isocyanate, metal, wood dust	Hairdresser, machine tool setter, motor vehicle mechanic
Irritants	Toxicological properties	Various sources	Chlorine gas, endotoxin, formaldehyde	Hairdresser, personal care worker, machine tool setter

The ACE JEM, an expert-rated job exposure matrix was developed in 2016 to the UK Standard Occupational Classification system, SOC 2000 [117]. All job codes were categorized into exposed or unexposed as well as level of exposure (not exposed, low,

medium, high exposure) and proportion of exposed workers (<5%, 5-19%, 20-49% and ≥50% exposed). Levels were based on percentage of UK workplace limits, and proportions were determined arbitrarily. Accidental exposures or the use of respiratory protective equipment were not included in levels of exposure. A complete mapping of ACE JEM from SOC 2000 to DISCO-88 was conducted. Major and sub-major group codes in the DISCO-88 did not exist in the SOC 2000 classification system. Instead, major and sub-major groups reflected the average of corresponding DISCO-88-unit groups in the entire population from CGPS.

The OAsJEM was developed for occupational asthma covering a total of 30 sensitizers or irritants for each job code classified as not exposed, medium or high exposed. *High exposure* was defined as at least 50% of the workers exposed at moderate to high intensity, *medium exposure* as low to moderate probability or low intensity of exposure and *not exposed* comprised of unlikely to be exposed with low probability and low intensity.

Exposure was accounted for differently in the studies to ensure power (table 5). In study I and III, mineral dusts, biological dusts, gases & fumes and VGDF from the ACE JEM were divided into no, low or high exposure. *Low exposure* comprised of a low level of exposure in more than 5% of workers and a medium level in 5% to 49% of workers exposed. *High exposure* comprised of a medium or high level with at least 50% of workers exposed to the inhalant. In study II, we used dichotomized and an indexed measure of exposure. Dichotomized exposure was included in the ACE JEM. The indexed measure was constructed by multiplying assigned values for levels of exposure with proportions of exposed; 0 (not exposed), 0.2 (low), 0.5 (medium), 1 (high) and proportions of exposed; 0 (0%), 0.2 (5%), 1 (30%) and 2.5 (75%). In study III, exposure to high molecular weight sensitizers, low molecular weight sensitizers and irritants were dichotomized into *exposed* (including both medium and high exposure) and *not exposed*.

Table 5. Measures of exposure

Dichotomized	Classes	Graded (units)
Not exposed	Not exposed	0
Exposed	Low	0.04; 0.1; 0.2; 0.5; 1
	High	1.25;2.5

In study I, exposure one year prior to study participation was used in main analyses and repeated with exposure the year of study examination. Exposure in study II was expressed as a mean annual exposure during follow-up. Mean annual exposure was calculated as the number of dichotomized exposed years or the sum of the exposed indexed years during follow-up divided by the total amount of years in the follow-up period. In study III, exposure was time-varying with year by year exposure during follow-up.

Job titles were assumed to be quite stable and not to vary across short periods of time. Last observation was maximally imputed five years prior to the missing job title in study II and III.

Outcomes

An overview of outcomes is shown in table 6.

Table 6. Outcomes

Outcome (study number)	Type of data	Brief description
Chronic productive cough (I)	Questionnaire	Answering 'yes' to the question: "Do you cough up sputum (in the morning or during the day) for as long as three months every year?"
Decline in lung function (II)	Physical examination	Annual decline in FEV_1 calculated from spirometries at two different time points
Exacerbations in obstructive lung disease (II)	Register-based	Prescription for oral corticosteroids, or emergency care unit assessment or hospital admission related to asthma or COPD during follow-up

Chronic productive cough was defined as self-reported cough with sputum for a minimum of three months of the year. *Decline in lung function* was based on prebronchodilatory spirometry conducted at each round of examination. Spirometry was repeated three times with the participant in a standing position and accepted if the difference between two tests was less than 5%, and the shape of the spirometry curves appeared correct. The highest obtainable values of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were recorded. Three different spirometers were used; 1) an electronic spirometer (Monaghan N 403; Littleton, CO, USA) in the first examinations of CCHS, 2) a dry wedge spirometer (Vitalograph, Maidenhead, UK) in examination round three and four of CCHS and the first ~14,000 participants of CGPS, and 3) an EasyOne™ Diagnostic Spirometer (ndd Medizintechnik, Zürich, Switzerland) in the fifth round of CCHS examinations and the remaining participants in CGPS. The first spirometer stopped functioning after the 1981–1983 examination, thus disabling direct comparison. We disregarded examination round three of the CCHS as FEV_1 values varied significantly from the remaining rounds of examinations. Decline in lung function was calculated as FEV_1 measured at the most recent round of examination minus FEV_1 at a previous round. To express annual decline, we divided by the number of years separating the two measures. *Exacerbations in obstructive lung disease* were identified in The Danish National Prescription Registry [119] and the Danish National Patient Register [120]. Collected prescriptions for oral corticosteroids (prednisolone and prednisone) and emergency care or admission with the following

diagnoses: 1. Primary diagnosis *chronic obstructive pulmonary disease* (ICD-10 code J44) and secondary diagnosis *pneumonia* (J13 or J18), 2. Primary diagnosis *asthma* (J45) or *status asthmaticus* (J46), 3. Primary diagnosis *respiratory failure* (J96) and secondary diagnosis *chronic obstructive pulmonary disease* (J44) or *asthma* (j45) or *status asthmaticus* (J46).

Statistical methods

Statistical analyses were performed in SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided P-value below 0.05 was considered statistically significant. Possible confounders were selected a priori. Sensitivity and supplementary analyses are described in detail in the papers.

We used mixed effects models with unstructured covariance in analyses with repeated numerical outcomes. 'Mixed' refers to the fact that both fixed and random effects were included in the model. The mean response was in this type of analysis modelled as subject specific (random effects) combined with effects shared by all individuals (the fixed effects) [121]. Unstructured covariance pattern was chosen, as it had the smallest value of Akaikes information criterion (AIC). Model assumptions were checked by plotted predicted populations means as well as residual plots to ensure that data followed a multivariate normal distribution.

Generalized estimating equations were (GEE) applied in repeated, binary outcomes. GEE was, opposed to mixed effects models, a population-level approach which fitted a marginal model to the longitudinal data. Regression parameters could be interpreted as population-averaged estimates while within subject correlation had been accounted for [122].

Multivariate Cox regression with age as underlying time scale and time-varying exposure was used to examine the association between exposure and exacerbations in asthma and COPD. The Cox proportional hazards function allowed for studying associations between a dichotomous dependent variable and independent variables. Hazards were assumed to be constant during the observed time period, and the proportional hazards assumption was assessed visually. We used age as an underlying time axis. Participants lost to follow-up (death or emigration) contributed until the last observed value.

Methods are summarized in table 7 below.

Table 7. Overview of methods

Paper	N participants	Covariates	Statistics	Outcome
I	5,210 (1973–83) 64,279 (2003–17)	Age group, sex, BMI, education, smoking status /tobacco consumption	Generalized estimating equations stratified by time period and smoking status	Chronic productive cough
II	16,144	Sex, height, weight, mean pack years/year, educational, baseline FEV_1	Mixed effects models stratified by cohort	Mean annual FEV_1 decline
III	7,768	Sex, BMI, education, smoking status, FEV_1 % predicted class, prior exacerbations	Cox regression with age as underlying time scale	Exacerbations of asthma and COPD

Abbreviations: N: number; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; BMI: body mass index.

Ethical considerations

Informed written consent was obtained from all participants. The cohort studies were approved by the Danish Ethical Committees and carried out according to recommendations of the Declaration of Helsinki.

Results

Study I

A total of 5,210 participants from the Copenhagen City Heart Study who participated between 1976 and 1983, and 64,279 from the General Population Study years 2003–2017 were included. Chronic productive cough was reported by 4–5% of non–smokers and 15–17% of smokers in two cohorts. The proportion of occupational exposed participants varied, with exposure categories and levels ranging from 41% of smokers in 1976–83 exposed to low levels of the composite variable of vapours, gases, dusts or fumes (VGDF) to 1 % of non-smokers in 2003–2017 exposed to high levels of gases & fumes.

In smokers, high levels of mineral dusts, gases & fumes, and VGDF were associated with chronic productive cough with odds ratios in the range of 1.2 (95% CI 1.0;1.4) to 1.6 (95% CI 1.3;1.9), and high levels of biological dusts only significantly associated with chronic productive cough in the 2003–2007 cohort, odds ratio 1.5 (95% CI 1.1;2.0). In non-smokers in the 1976–83 cohort, odds ratios were similar to those of smokers, but only high levels of vapours, gases, dusts or fumes (VGDF) (odds ratio 1.5 (95% CI 1.0;2.3) and low levels of mineral dusts (odds ratio 1.7 (95% CI 1.1;2.4) were significantly associated with chronic productive cough. We found no associations between exposures and chronic productive cough in non-smokers from the 2003–2017 cohort.

Study II

A total of 16,144 participants were followed for a mean of 9 years (SD 4). In dichotomized exposure, the proportion of exposed years varied from 7% of all years from 1980–1999 with exposure to biological dust to 36% of all years before 1980 with exposure to VGDF. Mineral dusts, biological dusts, gases & fumes and the composite variable vapours, gases, dusts or fumes (VGDF) exposures were not associated with change in FEV_1 in analyses of dichotomized exposure. Exposure to gases & fumes using the indexed measure of exposure was associated with an additional annual decline in FEV_1 of 6 mL/year (95% CI 2;11) per exposure unit in early years of the study period (1976–1990) and no significant associations in later years of the Copenhagen City Heart Study.

Study III

The study included 7,768 individuals with airflow limitation and/or self-reported asthma. At baseline, 2% were exposed to high levels of biological dusts and gases and fumes, while 5% were exposed to high levels of mineral dusts. Exposure at baseline to high and low molecular weight sensitizer and irritants ranged from 13–24%. Occupational exposure to the seven major categories of inhalant hazards and sensitizers were not associated with

exacerbations requiring oral corticosteroids or a hospital contact. Hazard ratios for low and high VGDF exposure were 1.0 (95% CI 0.8;1.1) and 1.0 (95% CI 0.8;1.3), respectively, and overall, within the range of 0.8 (95% CI 0.5;1.5) to 1.2 (95% CI 0.9;1.7).

Unpublished results

The most prevalent job titles differed from the first round of examinations in the Copenhagen City Heart Study to the Copenhagen General Population Study. Frequent occupations according to exposure are presented below in table 8.

Table 8. Frequent occupations according to indexed VGDF exposure and sex in first round of examinations in CCHS and CGPS in 35–55 years old participants

The Copenhagen City Heart Study		
	Males (4,874)	**Females (6,041)**
VGDF		
0	Office clerks (116), mail carriers and sorting clerks (78), messengers, package and luggage porters (58)	Office clerks (866), stock clerks (187), bookkeepers (76)
1.25	Construction and maintenance labourers (60), toolmakers and related workers (56), compositors, typesetters and related workers (53)	Cooks (94), hairdressers, barbers, beauticians, and related workers (12), hand-launderers and pressers (12)
2.5	Brewers-, wine and other beverage machine operators (70), painters and related workers (56), carpenters and joiners (43)	Helpers and cleaners in offices, hotels and other (208), brewers-, wine and other beverage machine operators (28), domestic helpers and cleaners (14)
-	Missing (66) Unemployed (1,083)	Missing (763) Unemployed (2,292)
The Copenhagen General Population Study		
	Males (31,177)	**Females (39,696)**
VGDF		
0	Computer system designers and analysts (1,161), technical and commercial sales representatives (776), directors and chief executives (673)	Secretaries (2,387), primary education teaching professionals (1,524), preprimary education teaching professionals (946)
1.25	Construction and maintenance labourers (245), plumbers and pipe fitters (210), motor vehicle mechanics and fitters (168)	Chemical and physical science technicians (245), cooks (210), hairdressers, barbers, beauticians, and related workers (168)
2.5	Carpenters and joiners (336), helpers and cleaners in offices, hotels and other establishments (141), painters and related workers (127)	Helpers and cleaners in offices, hotels and other (511), manufacturing labourers (59), painters and related workers (23)
-	Missing (3,684) Unemployed (3,382)	Missing (3,014) Unemployed (6,447)

Number of participants are represented by (). Indexed exposure values 0.04-1.0 not shown. Abbreviations: CCHS: The Copenhagen City Heart Study; CGPS: The Copenhagen General Population Study; VGDF: vapours, gases, dusts and fumes

Categories of exposure overlapped. Among all individuals who participated in CCHS or CGPS, 40% of all job codes were unexposed to dichotomized exposure to mineral dusts, biological dusts, gases & fumes, VGDF, high molecular weight, low molecular weight and irritants, while 14% were exposed to one category, 16% to two, 14% to three, 14% to four, 2% to five, and <1% to six categories of exposure.

The two cohort studies included in the thesis were both conducted in Copenhagen, the capital of Denmark. Below, exposure to VGDF and gases & fumes as well as skill levels are characterized for inhabitants living in the regions where study participants for CCHS and CGPS were approximately sampled from and from all Danish citizens aged 20 years and older.

Table 9. DISCO major groups in Denmark and regions where CCHS and CGPS were sampled from

	1981–1990		2007–2016		
	Denmark	**CCHS area**	**Denmark**	**CCHS area**	**CGPS area**
Total person years	29,257,245	2,080,151	31,678,042	2,482,603	1,936,636
Skill level (DISCO-88*)					
1 (9)	21%	18%	9%	7%	6%
2 (4 – 8)	49%	49%	46%	34%	31%
3 (3)	12%	14%	23%	24%	26%
4 (2)	12%	14%	17%	30%	28%
VGDF					
High	33%	25%	20%	11%	11%
Gases & fumes					
Low	10%	6%	8%	5%	6%
High	6%	4%	6%	3%	3%

*DISCO-88 major group. Abbreviations: CCHS: the Copenhagen City Heart Study; CGPS: the Copenhagen General Population Study

The areas where CCHS and CGPS were sampled from were comparable regarding skill levels and proportions of exposed. The proportion of exposed years were, however, generally higher in the entire country of Denmark with a larger fraction of people with lower skills levels.

Discussion

Main findings

Key findings are summarized below.

- Chronic productive cough was significantly associated with occupational exposures in smokers in recent years, and in both smokers and non-smokers in years before 1990.
- Exposure to mineral dusts, biological dusts, and VGDF was not associated with lung function decline. We found that mean annual indexed but not dichotomized exposure to gases & fumes was associated with lung function decline in years before 1990, while no associations were seen from 2003–2017.
- Exacerbations in asthma and COPD were not significantly associated with selected occupational inhalant exposure.

Findings in relation to other studies

Chronic productive cough

Chronic productive cough was associated with selected inhalant exposures in the 1976–83 cohort and among smokers in the 2003–2017 cohort confirming prior findings from general population and occupation and industry specific studies [33, 34, 36, 38-40, 42]. We found no significant associations among non-smokers in the 2003–2017 cohort which is consistent with at least one prior study [123]. Studies of occupational exposures and incident chronic bronchitis are few but findings indicate a time trend similar to our results: positive associations were reported in a study with follow-up from 1968–81, weak associations in a study with follow-up from 1985–1997 [124], while no associations were seen in a study with follow-up from 1991–2010 [43]. None of these studies, however, registered ongoing exposure with the risk of misclassification of exposure.

Lung function decline

Prior longitudinal, general population studies have largely reported that one or more inhalant exposures were associated with lung function decline [70-74, 76, 77], while a few others have not [38, 75]. In our study, indexed exposure to gases & fumes in the 1976–1990 cohort was associated with lung function decline. This is consistent with some prior studies [72, 77, 79] and conflicting with others [38, 70, 71, 73]. We did not find exposure to mineral dust to be associated with lung function in line with some previous studies [38, 72, 73] or to biological dusts exposure [71, 73]. However, other studies reported lung

function decline to be associated with mineral dusts [70, 71, 76, 79] or biological dusts [38, 70, 72].

The variable results might be explained by differences in assessment, timing and categorization of exposure, in available confounders and underlying differences in the populations. We relied on ongoing rather than delayed effects of occupational inhalant exposures on lung function decline. Thus, accounting for exposure during the entire follow-up period was essential and equally done in three other longitudinal, general population studies [71, 76, 77]. One recent study accounted for exposure during the entire follow-up but modelled lifetime cumulative pack-years (with imputed data on 8%) [71]. The study reported that 25 pack-years of smoking was associated with a statistically non-significant decline in FEV_1 of only 11 mL. This is inconsistent with most findings [125-127]. Consequently, results from this study should be used with caution. Another study included workers exposed to various inhalant hazards legally obliged to participate in health examinations [76]. An external reference group of 10,000 healthy volunteers was used. However, the healthy volunteers were likely to differ from the study group regarding other factors than the exposure which was not accounted for. The third study comprised of active smokers with COPD [77], and the results cannot be extrapolated to the general population without great caution if at all.

In contrast to these three studies, exposure assessment was either based on baseline information [70, 78, 79] with the risk of change of exposure during follow-up, on lifetime occupational history [72, 73, 75, 78] or determined either by a single job or by ever having had an exposed job during follow-up [38, 74]. Some occupational inhalant exposures resemble cigarette smoking which is the greatest risk factor for lung function decline [13]. Studies of former smokers compared to current and never smokers indicate that there is either no excess decline in FEV_1 among ex-smokers or quitters compared to never smokers [128] or much smaller differences of only 2 mL excess decline per year between former and never smokers [129]. Accounting for smoking as ever/never smoker, cigarettes smoked before but not during follow-up or using smoking status at baseline in longitudinal analyses of smoking and lung function decline could attenuate true associations. Similar risks may be true in occupational studies. However, the assumption that ongoing exposure is of importance rather than ever being exposed during a lifetime differs from other types of occupational lung diseases. An example is mesothelioma, where a small amount of asbestos fibres once inhaled might cause cancer decades later.

Exacerbations of asthma and COPD

We found no statistically significant association between occupational exposure and moderate to severe exacerbations. Including only self-reported asthmatics, low levels of gases & fumes were associated with exacerbations with a hazard ratio of 1.6 (95% CI 1.1;2.3) whereas high exposure to gases & fumes showed a statistically non-significant

hazard ratio of 1.0 (95% CI 0.6;1.6). The literature is sparse concerning occupational inhalant hazards and exacerbations of asthma and COPD. In line with our results, JEM assigned exposure to agents with high molecular weight, low molecular weight or irritating properties were not associated with exacerbations of asthma [110]. Positive associations between asthma exacerbations and self-reported exposure to biological dust, and inconsistent results concerning mineral dust have been reported [110, 111]. The odds of exacerbations requiring use of health care were found to be greater in COPD patients with an intermediate/high risk of occupational exposure [112].

Exposure, exacerbations or both were in all studies self-reported with risk of recall bias which might contribute to differences. Additionally, the definition of asthma varied between the studies. In one study, individuals with asthma were defined based on a doctor diagnosis of asthma and symptoms of asthma within the last year and/or current asthma medication [111]. In comparison, our study included both individuals with current and former asthma which might explain the inconsistencies.

Strengths and limitations

Major strengths and limitations are summarized below with emphasis on exposure assessment and lung function decline. Detailed discussions are presented in the papers.

Design

The large, random samples of the Danish population with ethnic homogeneity was a major strength. Generalizability to other populations should, however, be done with caution. The uniform use of questionnaires enabled assessment over a long period of time in study I. Relatively long follow-up in study II, and minimal loss to follow-up due to registry-based diagnoses in study III were strengths. The study design allowed for exploring temporal associations but is inferior to randomized controlled trials (RCT) in establishing causality. RCT are inapplicable in most occupational studies concerning lung disorders. Instead, industry or occupation specific studies are alternatives to our study design. They offer more precise exposure classification, but results are difficult to extrapolate to the general population.

Missing data

Missing data was a key limitation. Generally, missingness is characterized as *missing completely at random (MCAR)* when there are no systematic differences between the observed and missing data, *missing at random (MAR)* when systematic differences depend on known variables in the observed data (i.e. sex), and *missing not at random (MNAR)* meaning that systematic differences between the observed and missing data are explained

by unobserved data (i.e. the missing value itself) [130]. Methods for managing missing data are numerous i.e. complete-case-analyses, and multiple imputation [130]. In studies with repeated measures, last observation carried forward, mean value substitution and missing indicator method are applicable [131, 132].

We used complete case analyses in paper I with the risk of loss of power and less precise estimates, if data were MCAR [133], and bias if the missing data were MAR or MNAR [134]. We did not perform alternative analyses, and this was considered to be a key limitation.

In study II and III, we carried the last observation forward in case of missing job titles in employed years. The method of last observation carried forward and thus exchanging a missing value with the last recorded is generally not recommended [135]. A major problem is that each missing observation is replaced by a single value, thus gaining the same status as the observed observations [136]. As a result, estimates may be biased and confidence intervals too narrow [131, 132, 136]. In Denmark, small companies with less than 10 employees are not legally obliged to report occupational information [116] and thus missingness might be associated with either sex (MAR) or exposure status (MNAR). In participants with missing job titles, the proportion of exposed in the last known job title were generally higher than those with complete data. In years following one or several missing job titles, the proportion of exposed did, however, not differ from the year carried forward. This was expected, as occupation is generally robust. Although possible, it is unlikely that exposure status differed only in missing years, and thus the effects on estimates and confidence intervals were considered to be minor.

Not all DISCO-88 codes were complete. In study II, DISCO-88 codes were only available with all four digits in 66% of all employed years, three digits in 29%, two digits in one % and one in four % of all years. Completeness improved with time. This could result in misclassification primarily in early years of the study period.

Non-responders and the healthy worker effect

Participation rates were relatively low ranging from 43% in the CGPS to 74% in the first round of CCHS. Self-selection into cohort studies either due to concerns of health issues, or more time to participate if better socioeconomic position, might limit the generalizability of our results. Although the sample sizes were quite large, participants were sampled from areas of Denmark with a lower proportion of exposed individuals. Additionally, it is possible that the exposed occupations differed from those of rural areas.

Differential loss to follow-up in paper II was a concern. The study involved individuals who participated at least twice. A study of individuals from the CCHS showed that non-participants in the fourth round of examinations had more rapid FEV_1 declines than respondents [48]. If those with a more rapid decline in FEV_1 were more likely to be

exposed, associations could be attenuated. Characteristics regarding exposure of included participants and those lost to follow-up did, however, not differ.

The healthy worker effect is a major challenge in occupational research. It denotes that individuals who stay employed are healthier than those who do not [18]. Since concomitant exposure was an underlying requirement in our studies, and individuals were not chosen based on occupational status, the healthy worker effect was thought to be of minor importance.

Information bias

Information bias is based on errors in measuring exposure or outcome. Misclassification due to measurement error is divided into non-differential and differential misclassification. Non-differential misclassification is in occupational research often characterized as classical or Berkson measurement error [137, 138]. Berkson type error might occur when using a group average of exposure. The true exposure level of each worker within the same job title or category is believed to vary around the assigned exposure level. While the effect of classical, non-differential misclassification of exposure might attenuate associations, Berkson type is thought to result in little or no error [137]. This has, however, been disputed since the JEM assigned exposure value is only assumed to be the true exposure [139]. If the assigned exposure is different from the true exposure in a job category, all workers in that job will be affected. Thus, classical measurement error is present [139]. Differential misclassification occurs, when error is more likely to occur in one of the groups being examined.

Misclassification of exposure

Measurement error in exposure may have affected inference drawn from the studies. Depending on the type of error, estimates might be biased or imprecise. Advantages and limitations in JEM-based exposure assignment have already been stated. Most importantly, JEM based exposure estimates only reflect a fraction of the entire range of exposure. Exposure estimates are, however, difficult to extrapolate to other individuals in similar jobs even in studies with individual measurements of airborne exposures. JEMs are often based on expert judgement with limited evidence to substantiate the classification [140]. The ACE JEM has previously been used in studies of occupational exposure and COPD [141] and type-2 diabetes mellitus and dementia [142]. A study conducted to evaluate the suitability of the ACE JEM in dust, fumes and diesel exhaust particle exposure has recently been published [143]. The study used exposure data from published literature as well as assessment by an(other) expert. Highly exposed and unexposed job titles were reported to be reliable, whereas low and medium exposure were less reliable [143]. The conclusion reflects that most studies with available measurements of exposure are conducted in high exposed trades. Thus, the implications are possibly true for most general population JEMS

within the same area. The ACE JEM was not created to access exposures before the year 2000 and disregarded occupational passive smoking. Consequently, misclassification of jobs held before year 2000 might be present.

In using the OAsJEM, researchers were suggested to perform an expert re-evaluation step. We, however, did not make any changes to either ISCO or exposure group codes in the OAsJEM. This was 1) to secure reproducibility of results, 2) because additional information on job tasks to improve the precision of the JEM were not available, and 3) as the suggested expert re-evaluation included changes to approximately 20% of all ISCO-88 job codes, it was considered too extensive. As a result, misclassification might have occurred.

Since there is no gold standard to exposure assessment, case-by-case expert reporting is by some considered best practice [16, 17, 140]. The exposure of each individual is evaluated based on additional data on each employment including company and tasks, production procedures or time period. However, this method also involves expert opinions, and comparisons essentially assess the agreement between two (or more) experts. Also, the case-by-case method depend to some extent on questionnaire or self-reported data concerning work conditions and tasks which are prone to non-differential and differential reporting error [16]. Another alternative to expert assigned JEMS is JEMs with incorporated measurements of exposure. These are, however, often expensive and time-consuming to build and still cannot account for differences within the same job code. Lack of historical measures, differences in methods for sampling and analyses, and reasons for collecting the samples are other weaknesses [144].

Misclassification of outcomes and selected covariates

The quality of spirometry depends on the participant, technician and the spirometer. Yet, standards for test acceptability, instructions and for instrument calibration were followed in both cohorts. Lung function measurements fluctuate around the true value [145] and may have decreased the precision of our estimates. The long follow-up time minimized the within-person variation of FEV_1 [146]. Although differences in spirometers used over time may introduce systematic bias, effects were considered to be minor and to affect exposed and unexposed equally.

We defined airflow limitation based on recommendations by the Global Initiative for Chronic Obstructive Lung Disease [27] as FEV_1/FVC ratio < 0.70, although postbronchodilator values were not available. Another method for assessing airflow limitation is by comparing FEV_1/FVC to lower limit of normal (LLN). Lower limit of normal (LLN) represents the lower 5% of FEV_1, FVC and FEV_1/FVC measured in healthy, non-smokers according to sex, age, height, and race. A fixed value of FEV_1/FVC may result in underestimation of airflow limitation in individuals younger than 45 years old [147] and overestimation in the elderly [148-150], but is more accurate in identifying individuals in

risk of COPD-related hospitalization and mortality [151]. Since airflow limitation was only used as an inclusion criterium in study III and the mean age of participants at study inclusion was 50 years old (SD 7), this was considered to be of minor importance.

In study III, registry data were used to define exacerbations. Strengths have already been accounted for. The content of the Danish Patient Register has changed through times, and coding practise is to a certain degree influenced by the payment rate attached to each diagnose-related group. Also, COPD has been found to be under-recorded following admissions for pneumonia and respiratory failure [152]. Non-differential misclassification of exacerbations may have weakened the associations.

Information on smoking patterns and asthma were obtained through questionnaires. The method has shown high specificity in asthma [153] but some individuals with self-reported asthma might instead have COPD [27]. COPD and asthma were used to indicate airflow obstruction. Possible misclassification would only have affected our sensitivity analyses and was considered to be non-differential. Validation of self-reported historical smoking patterns is difficult if possible. Self-reported smoking has shown trends of underestimation when compared with serum measurements of cotinine which is a nicotine metabolite [154, 155]. Underestimation of smoking would affect both exposed and unexposed with the risk of non-differential misclassification.

In more recent studies and guidelines, mucus production is not included in the definition of chronic cough, and the time span is a minimum of eight weeks [29]. The associations might be different when evaluating chronic cough and occupational exposures.

Confounding

A confounder is associated with both the exposure and outcome and is not on the causal pathway between exposure and outcome. Residual confounding might occur when confounders are not accounted for correctly [137]. A major strength of our studies was, in contrast to many register-based studies, the accessibility to potential confounders.

We chose confounders prior to our analyses and used causal directed acyclic diagrams (DAGs) to minimize risk of adjusting for a mediator as proposed by others [156].

In study II, we adjusted for baseline FEV_1 which is controversial and by some believed to result in over-adjustment. Excluding baseline FEV_1 from our analyses did, however, not change the direction of our estimates. Also, we adjusted for weight but not weight change which has been shown to be associated with decline in FEV_1 [157]. Third, as a proxy for socioeconomic status (SES), we used longest obtained education. This only to some degree accounts for SES with the risk of residual confounding. Still, it is difficult to account completely for SES, as it is highly correlated to job type and exposure. Our crude estimates in paper II were, however, very close to the adjusted estimates, indicating a low risk of residual confounding and over-adjustment.

In reverse causation, the outcome precedes and causes the exposure. As we were not able to secure temporality in study I, chronic productive cough could lead to avoiding future occupational airborne exposure. As a result, associations might be attenuated. However, participants in study I who reported chronic productive cough were not more likely to differ in exposure status five year prior to inclusion than those who did not report chronic productive cough, indicating only minor risk of reverse causation.

Conclusion and perspectives

In conclusion, current knowledge on occupational inhalant hazards and lung function decline from longitudinal general population studies is limited and conflicting. Our results suggest that present levels of selected occupational exposures are not causally related to lung function decline in individuals similar to our participants. Occupational exposure to the selected categories was not associated with exacerbations of asthma and COPD, and from 2003–2017, only associated with chronic productive cough in smokers.

Our findings contrast with the large amount of studies indicating that occupational inhalant hazards are associated with COPD. In studies of COPD, estimation of cumulative occupational exposures seems appropriate. However, exposure levels have changed over the last decades, and lifetime cumulative exposure rarely, if at all, is able to account for this. The lack of association between ongoing occupational exposures and lung function decline in our study could be explained by declining occupational inhalant exposure levels, or a failure to show the true association due to limitations of our study. Most importantly, exposure assessment in our study was not based on personal exposure measurements due to costs and feasibility. Large variations exist on all levels: between job titles assigned to the same type and level of exposure, within each job title due to different tasks performed, and even within each individual due to job tasks varying over time. Thus, measurement error in occupational exposure might have resulted in incorrect conclusions. Alternatively, differences might be explained by poor adjustment for confounding and misclassification of occupational exposure in some prior studies. Although attempts have been made, the effects of lifetime socioeconomic status are difficult to disentangle from those of lifetime occupational exposures with the risk of residual confounding.

In future studies, exposure assessment might be refined by quantitative measurements and time specific values to improve performance. The effects of occupational airborne exposures in respiratory disease, however, depend not only on inhalant hazard but also on factors inherent in the individual, including genetic susceptibility, lifestyle choices (such as smoking) and comorbid disease [158]. Medical surveillance with repeated questionnaires and longitudinal spirometry in the occupational setting in Denmark is limited. The difficulties in choosing the appropriate workers for surveillance, the costs, requirement of at least 5 years of follow-up and variability in testing are major challenges [159, 160]. Instead large population studies such as CGPS might provide alternatives reflecting the general population and not only high-risk trades. The study design allows for repeated measures possibly with and without periods of exposure within the same individual. Future studies are required to clarify whether the selected occupational inhalant exposures are

causally related to chronic productive cough, lung function decline, and exacerbations of asthma and COPD.

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Appendix

Papers I, II, III

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ORIGINAL ARTICLE

Chronic productive cough and inhalant occupational exposure–a study of the general population

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Abstract

Purpose Occupational inhalant exposures have been linked with a higher occurrence of chronic productive cough, but recent studies question the association.

Methods We included participants from two general population studies, the Copenhagen City General Population Study and the Copenhagen City Heart Study, to assess contemporary (year 2003–2017) and historical (1976–1983) occupational inhalant hazards. Job titles one year prior to study inclusion and an airborne chemical job-exposure matrix (ACE JEM) were used to estimate occupational exposure. The association between occupational exposures and self-reported chronic productive cough was studied using generalized estimating equations stratified by smoking status and cohort.

Results The population consisted of 5210 working individuals aged 20–65 from 1976 to 1983 and 64,279 from 2003 to 2017. In smokers, exposure to high levels of mineral dust, biological dust, gases & fumes and the composite variable vapours, gases, dusts or fumes (VGDF) were associated with chronic productive cough in both cohorts with odds ratios in the range of 1.2 (95% confidence interval, 1.0;1.4) to 1.6 (1.2;2.1). High levels of biological dust were only associated with an increased risk of a chronic productive cough in the 2003–2017 cohort (OR 1.5 (1.1;2.0)). In non-smokers, high levels of VGDF (OR 1.5 (1.0;2.3)) and low levels of mineral dust (OR 1.7 (1.1;2.4)) were associated with chronic productive cough in the 1976–1983 cohort, while no associations were seen in non-smokers in the 2003–2017 cohort.

Conclusion Occupational inhalant exposure remains associated with a modestly increased risk of a chronic productive cough in smokers, despite declining exposure levels during the past four decades.

Keywords Occupation · Work · Chronic cough · Chronic bronchitis

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Introduction

Chronic productive cough (chronic bronchitis) is traditionally defined as cough and sputum expectoration for at least three months in two consecutive years (Irwin et al. 2006) and is a validated measure in respiratory epidemiology (Fletcher et al. 1974). It is prevalent in the general population (Cerveri et al. 2001; de Oca et al. 2012; Ferre et al. 2012) and associated with acute respiratory exacerbations, an excess loss of lung function and marginally higher mortality (Lange et al. 1990b; Vestbo et al. 1996). The main risk factor for chronic productive cough is tobacco smoking, and other causes include gastroesophageal reflux, rhinosinus disease and occupational inhalant hazards. Occupational inhalant exposures are often divided into subgroups such as vapours, gases, dusts (mineral and biological) and fumes, or expressed as a combined measure of all these.

In 2019, the estimated occupational attributable fraction for chronic productive cough was 13% (Blanc et al. 2019). Occupationally exposed workers are not routinely screened for chronic productive cough but general practitioners are advised to question patients with a chronic productive cough about inhalant hazards in the workplace (Irwin et al. 2006). Health records on chronic cough and occupational hazards from general practitioners are often difficult (if not impossible) to assess. Established associations between a chronic productive cough and occupational exposures largely derive from general population studies (Axelsson et al. 2016; Doney et al. 2014; Hansell et al. 2014; Jaen et al. 2006; Lange et al. 2003; Sunyer et al. 2005) supported by numerous smaller industry-specific studies (Barber and Fishwick 2008). However, while exposure to vapours, gases, dusts or fumes in the workplace was found to be positively associated with chronic bronchitis in a meta-analysis with odd ratios in the range of 1.2 (1.1;1.4) to 1.4 (1.3; 1.5) (Sadhra et al. 2017), a recent, longitudinal study found that incident chronic bronchitis was not increased in any of these exposure groups (Lytras et al. 2019). Most occupational inhalant exposures have declined substantially in industrialized countries within the last decades (Creely et al. 2007). The improvements are suggested to be ongoing, as a recent study monitoring European industrial minerals sectors between 2002 and 2016 reported a 9% annual decline in respirable dust (Zilaout et al. 2020). Consequently, some work-related inhalant hazards may have reached a level where chronic productive cough is no longer a risk.

Our primary aim was to assess if the established higher risk of chronic productive cough related to occupational exposure to vapours, gases, dusts and fumes is still imminent given the substantial reduction in exposure levels and overall change in the past 40 years.

Methods

Population

The study population (Supplementary Fig. F1) was selected from two Danish population-based cohorts: The Copenhagen City Heart Study and the Copenhagen General Population Study. The first round (1976–78) of the Copenhagen City Heart Study included 14,223 individuals randomly selected from specific areas of Copenhagen. During 1981–83, out of the 14,223 individuals previously enrolled, 11,123 were reexamined, and 1563 new subjects were enrolled. The Copenhagen General Population Study is a cohort initiated in 2003 with continuous follow-up. In both cohorts, all individuals were aged 20 years or older during enrollment. At each visit, the individuals in both cohorts completed a questionnaire, a physical examination, and clinical tests including spirometry.

The studies were approved by Danish Ethical Committees (KF-01-144/01, H-KF-01-144/01) and were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

In the present study, we excluded persons who at study participation were older than 65 years or unemployed the year before (Supplementary Fig. F1). Individuals with missing information regarding chronic productive cough, job title or other covariates were also left out of the analyses.

Chronic productive cough and spirometry

Participants were at every visit asked, "*Do you cough up sputum (in the morning or during the day) for as long as three months every year?*". Questions regarding smoking status and self-reported asthma were also included. Lung function was obtained using spirometry. An electrical spirometer (Model N 403, Monaghan, Littleton, Colorado, USA) was applied in The Copenhagen City Heart Study. In the Copenhagen General Population Study a Vitalograph (Maids Moreton, Buckinghamshire, United Kingdom) was used in the first 14,625 participants and an EasyOne Diagnostic Spirometer (ndd Medizintechnik, Switzerland) in the remaining participants. Both the electrical spirometer and the Vitalograph were calibrated daily, while the EasyOne spirometer was verified with a 3-L syringe regularly. Prebronchodilator forced expiratory volume in the first second of expiration (FEV_1) and forced vital capacity (FVC) were measured with the participant in a standing position. A valid test included at least two measurements which did not differ by more than 5% and a correct visual appearance of the

spirometry curves. The largest volumes of FEV_1 and FVC were recorded.

Occupational inhalant exposure

Job titles and labour market affiliation at the examination date and one year before assessment of outcome were obtained by linkage with the Danish Occupational Cohort with eXposure (DOC*X), a national database involving all wage earners in Denmark with at least one year of employment in the period 1970–2017 (Flachs et al. 2019; Petersen et al. 2019). Each year in the DOC*X database provided information on employment status (employed/not employed) and job codes according to the Danish version of the International Standard Classification of Occupation (DISCO-88). The DISCO-88 codes were linked to an expert-rated job-exposure matrix, the airborne chemical job-exposure matrix (ACE JEM) (Sadhra et al. 2016). The ACE JEM is based upon expert ratings by occupational exposure assessors. It classifies exposure into the type of inhaled pollutant, proportion of workers exposed and intensity (level) of exposure in each of the UK SOC 2000 classification codes (Statistics 2000). Intensities include no exposure, low intensity of exposure (defined as more exposed than the general background occupational level but less than 10% of the U.K. workplace exposure limit), medium and high intensity (equivalent to 10–50% and 50% or higher than the U.K. workplace exposure limit). The proportion of exposed workers within each job code is categorized as < 5%, 5–19%, 20–49% and ≥ 50% of all workers in the specific job code. A complete mapping of the DISCO-88 codes to the UK SOC 2000 was performed. The hierarchy in the UK SOC 2000 differs from DISCO-88, and most of the major and sub-major group codes in the DISCO-88 had no matching SOC 2000 code. JEM values for these were assigned based on the population distribution of the corresponding DISCO-88 unit groups.

Exposure categories for this study were constructed based upon a combination of ACE JEM assigned probability and intensity of exposure. If the ACE JEM assigned the study participant's job at low intensity in more than 5% of workers or medium intensity in 5–49% of workers exposed, it was categorized as low exposure. High exposure was defined as those with medium or high intensity, with at least 50% of workers exposed to the inhalant. The remaining job codes were classified as not exposed. We selected the following, most prevalent exposure types: mineral dust, biological dust, gases & fumes and their composite variable vapours, gases, dusts or fumes (VGDF). VGDF intensity and probability were in the ACE JEM assigned the highest values of the components. The ACE JEM covers working conditions in the U.K. in the period 2000–2013 and does not contain a time axis. As exposure intensities and proportions have declined significantly since the 1970ies, we analyzed the two cohorts separately to investigate time trends in the associations.

Other covariates

Information from the questionnaire was used to categorize study individuals as follows; age (< 50; ≥ 50 years old), smoking (never smoker; former smoker; light smoker < 15 g of tobacco/day; moderate smoker 15– < 25 g of tobacco /day; heavy smoker ≥ 25 g of tobacco /day), highest completed education (elementary school; high school; academic education) and body mass index (BMI). A ratio of pre-bronchodilator forced expiratory volume in 1 s (FEV_1) divided by forced vital capacity (FVC) below 0.70 served as a proxy for chronic obstructive lung disease (COPD). Post-bronchodilator values were not available. Asthma was based on a self-reported doctor-diagnosed asthma.

Statistical analyses

Categorical variables were summarized using numbers and proportions and continuous variables by arithmetic means (standard deviation).

Associations between inhalant occupational exposure the year before study participation and presence of chronic productive cough were examined separately for each cohort using generalized estimating equations (GEE), including both individuals with one and two study visits. The method estimates the population average effect size while accounting for within-subject correlation. The results are presented as odds ratios, OR (95% confidence intervals, CI).

The association of occupational inhalant agents on chronic productive cough interacted with that of smoking (exposure*smoking) and all models were, therefore, stratified by current smoking status (smoker, non-smoker). We adjusted for age, sex, educational level, body mass index in all models, and additionally for smoking status (never or former smoker) in non-smokers and daily tobacco consumption in smokers (light, moderate, heavy smokers). Self-reported asthma and prebronchodilator $FEV_1/FVC < 0.70$ were both possible mediators, confounders and effect modifiers and were tested as independent variables and in interaction analyses.

Sensitivity analyses were performed on the subsample of individuals with two test points to test the strength of the estimates in a design with only repeated measures and in analyses replacing job titles the year before study participation with jobs held at the year of the study examination.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). *P*-values were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics stratified by smoking and participation period are presented in Table 1. The population consisted of 5210 working individuals aged 20–65 from the 1976 to 1983 Copenhagen City Heart Study (CCHS) and 64,279 from the 2003 to 2017 Copenhagen General Population Study (CGPS) with mean baseline ages of 48 (range 21–65) and 50 (20–65) years, respectively. A total of 3096 individuals participated twice between 1976 and 1983, and 7101 between 2003 and 2017 with complete exposure, outcome and covariate data at both visits. Smoking was more prevalent at baseline in the 1976–1983 cohort (68%) than in the 2003–2017 cohort (17%). Smokers more frequently reported chronic productive cough than non-smokers (1976–983 CCHS: 5% of non-smokers, 15% of smokers; 2003–2027 CGPS: 4% of non-smokers, 17% of smokers). The proportion of occupationally exposed was, in general, higher among smokers than non-smokers within the same cohort (Table 2). The occupational inhalant exposure levels at first examination in individuals with two study examinations did not differ from those in the full study population.

Smoking interacted with the association of vapours, gases, dusts or fumes (VGDF) exposure on chronic productive cough ($P < 0.05$ in the 1976–1983 cohort and $P < 0.002$ in the 2003–2017 cohort), and all analyses were therefore stratified by current smoking status. The fully adjusted models stratified by smoking status are presented separately for each cohort in Supplementary Tables S1 and S2. Age above 50 years was strongly associated with chronic productive cough in both cohorts. The odds ratio for chronic productive cough in heavy smokers was approximately 11 times as high as in never smokers. Exposure to mineral dust, biological dust and gases & fumes were greatly overlapping: in 95 percent of observations assigned to high exposure level, exposure to at least two types of exposure contributed (results not shown).

Table 1 Baseline characteristics according to study participation

	Period 1 (1976–1983) (*N* = 5210)	Period 2 (2003–2017) (*N* = 64,279)
Age, years	48 (21–65)	50 (20–65)
Male sex	2861 (55)	28,235 (44)
Smoking status		
Never	887 (17)	28,877 (45)
Former	804 (15)	24,407 (38)
Light smoker	1344 (26)	5159 (8)
Moderate smoker	1600 (31)	4606 (7)
Heavy smoker	575 (11)	1230 (2)
Education		
Elementary	3425 (66)	7527 (12)
High school	1513 (29)	38,584 (60)
Academic	266 (5)	18,040 (28)
BMI, kg/m^2	24.7 (3.9)	25.9 (4.3)
Pulmonary findings		
Self-reported asthma	88 (2)	3886 (6)
FEV_1, liters	2.9 (0.8)	3.3 (0.8)
FVC, liters	3.5 (1.0)	4.3 (1.0)
FEV_1/FVC	0.8 (0.1)	0.8 (0.2)
FEV_1/FVC < 0.70	663 (13)	6781 (11)

N number of individuals, *BMI* body mass index, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity. Data are presented as number (range), number (%) or mean (standard deviation)

Table 2 Occupational exposure at first examination according to period and smoking status

	Period 1 (1976–1983)		Period 2 (2003–2017)	
	Non-smoker	Smoker	Non-smoker	Smoker
Vapours, gases, dusts or fumes				
No	805 (48)	1407 (40)	36,250 (68)	6572 (60)
Low	611 (36)	1444 (41)	13,008 (24)	2812 (25)
High	275 (16)	668 (19)	4026 (8)	1611 (15)
Mineral dust				
No	1228 (72)	2411 (69)	43,941 (82)	8603 (78)
Low	317 (19)	763 (22)	7301 (14)	1420 (13)
High	146 (9)	345 (10)	2042 (4)	972 (9)
Biological dust				
No	1357 (80)	2788 (79)	44,794 (84)	9114 (83)
Low	266 (16)	559 (16)	7909 (15)	1665 (15)
High	68 (4)	172 (5)	581 (1)	216 (2)
Gases & fumes				
No	1492 (88)	2990 (85)	50,016 (94)	9947 (90)
Low	145 (9)	402 (11)	2342 (4)	660 (6)
High	54 (3)	127 (4)	926 (2)	388 (4)

Data are presented as number (%)

Occupational inhalant exposures and chronic productive cough

Associations between occupational inhalant exposures and chronic productive cough are shown in Table 3. In smokers, high levels of all types of exposure except for biological dust in the 1976–1983 cohort were associated with chronic productive cough with odds ratios ranging from 1.2 to 1.6. In addition, odds ratios in non-smokers in the 1976–983 cohort largely resembled those of smokers, but only high levels of vapours, gases, dusts or fumes (VGDF) and low levels of mineral dust in non-smokers reached statistical significance with odds ratios of 1.5 (95% CI 1.0;2.3) and 1.7 (1.1;2.4), respectively. No tendencies or significant associations were found in non-smokers from 2003 to 2017.

Table 3 Odds ratios for chronic productive cough and exposure according to period and smoking status

	Period 1 (1976–1983)		Period 2 (2003–2017)	
	Non-smoker	Smoker	Non-smoker	Smoker
Vapours, gases, dusts or fumes				
Low	1.2 (0.8;1.7)	0.9 (0.8;1.1)	1.0 (0.9;1.1)	1.1 (1.0;1.3)
High	1.5 (1.0;2.3)	1.3 (1.1;1.6)	1.0 (0.9;1.1)	1.3 (1.1;1.5)
Mineral dust				
Low	1.7 (1.1;2.4)	1.1 (0.9;1.3)	1.0 (0.9;1.1)	0.9 (0.8;1.1)
High	1.5 (0.9;2.5)	1.6 (1.3;1.9)	1.1 (0.9;1.3)	1.2 (1.0;1.4)
Biological dust				
Low	1.0 (0.6;1.5)	0.9 (0.7;1.1)	0.9 (0.8;1.1)	1.2 (1.0;1.3)
High	1.4 (0.7;2.9)	1.2 (0.9;1.6)	1.2 (0.9;1.6)	1.5 (1.1;2.0)
Gases & fumes				
Low	1.0 (0.6;1.6)	0.9 (0.7;1.1)	0.9 (0.8;1.1)	1.0 (0.9;1.3)
High	0.6 (0.2;1.5)	1.6 (1.2;2.1)	1.1 (0.9;1.4)	1.3 (1.0;1.6)

Generalized estimating equations on exposure and chronic productive cough. All odds ratio (95% confidence interval) are adjusted for age group, sex, body mass index, and educational level, and additionally for smoking status (never or former smoker) in non-smokers and daily tobacco consumption in smokers (light, moderate, heavy smokers). Reference is non-exposed to the category of exposure

The most prevalent occupations in the 2003–2017 cohort did not differ between smokers and non-smokers but varied across exposure categories. Construction and maintenance labourers, and helpers and cleaners were the most prevalent occupations exposed to high levels of mineral dusts; carpenters and joiners and building construction labourers the most frequent in high-level biological exposure, and cooks and motor vehicle mechanics and fitters in high-level gases & fumes exposure.

Stratification by or adjusting for asthma and FEV_1/FVC < 0.70 did not markedly alter the main associations. No significant interactions on chronic productive cough were found between occupational inhalant exposure and sex, exposure and self-reported asthma or exposure and FEV_1/FVC < 0.70 (data not shown).

Sensitivity analyses

Restricting the population to individuals with repeated measurements did not change the direction of any of the statistically significant associations (Supplementary Table S3). High levels of all exposure types except gases & fumes were associated with chronic productive cough in non-smokers from 1976 to 1983. We were not able to conduct the analyses on the subtypes of exposure in smokers from 2003 to 2017 due to too few exposed individuals.

We stratified the study populations into two smoking categories (non-smoker and smoker). All models were repeated with three smoking groups (never smokers, former smokers, current smokers), which showed similar associations of occupational inhalant exposure in chronic productive cough in former and never smokers and with no overall change in our conclusions.

To make sure that the exposure preceded the outcome we used the individuals' job title in the year prior to the examination., All models were also run with exposure from the job title from the actual year of study participation with no change in the main findings.

Discussion

In this study, high levels of work-related mineral dust, biological dust, gases & fumes and the composite variable vapours, gases, dusts or fumes were associated with chronic productive cough in smokers in both 1976–83 and 2003–2017, with high levels of biological dust borderline significant among smokers in the 2003–2017 cohort. In the 1976–1983 cohort only, the same tendencies were found in non-smokers. In total, chronic productive cough was prevalent in 4% of non-smokers and 17% of smokers. Smoking status and intensity were strongly associated with chronic productive cough as an indication of the validity of study design and data.

A recent meta-analysis of job exposure matrix-based studies showed odds ratios for chronic bronchitis and exposure to either vapours, gases, mineral or biological dust or fumes within the range of 1.2–1.6 (Sadhra et al. 2017), which is in line with our findings in smokers. The meta-analysis was based on both general population and work-based studies with a time of exposure ranging from 1960 to 2010. Exposure to high but not low levels of the composite variable vapours, gases, dusts or fumes (VGDF) was associated with chronic bronchitis in both the meta-analysis and our study.

General population cohorts with longitudinal data on chronic productive cough and occupational inhalant exposures, which are based on different cohorts are few (Krzyzanowski and Jedrychowski 1990; Lytras et al. 2019; Skorge et al. 2009). A recent analysis of the incidence of chronic bronchitis according to occupational exposures (Lytras et al. 2019) found that none of the selected inhalant exposures were associated with incident chronic bronchitis in comparable age groups to the present study. The study was initiated in 1991–1993 and followed-up around the year 2000 and/or 2010. Possible exposure was recorded up to several years prior to the outcome. Chronic productive cough is, in many cases, dependent on the presence of the trigger (Allinson et al. 2016). Studies have shown that chronic bronchitis resolves in the majority of smokers who quit smoking (Brown et al. 1991; Lange et al. 1990a) and in half of these within one month (Wynder et al. 1967). Even in patients

with mild to moderate chronic obstructive pulmonary disease, changes in respiratory symptoms generally occurred within the first year after quitting smoking (Kanner et al. 1999). The different results found by (Lytras et al. 2019) might be explained by way of assessing exposure. In addition, the study did not stratify based on smoking status, which might contribute to the observed differences.

Also in support of our findings, a study by (Zock et al. 2001) based on the same cohort as mentioned above but with only cross-sectional data and exposure primarily defined by current occupation found no association between chronic productive cough and exposure to vapours, gases, dusts or fumes in never- or ex-smokers, but a prevalence ratio of 1.3 (0.9;1.8) and 1.7 (1.2;2.4) in current smokers exposed to low and high levels of VGDG respectively (Zock et al. 2001).

Our study suggests that some exposures in 2003–2017 are too weak to be associated with chronic productive cough without the presence of another irritant like cigarette smoking. In our study, only a small proportion of non-smokers in the 1976–1983 cohort were occupationally exposed, and the insignificant results among non-smokers may therefore alternatively be explained by lack of power. High levels of biological dust were only borderline significant in smokers in the 1976–1983 cohort, which is most likely due to lack of power as well. The odds ratios in exposed smokers in the 1976–1983 cohort were marginally higher than in the contemporary 2003–2017 cohort as expected due to higher levels of occupational inhalant exposure at the workplace in 1976–1983 compared with 2003–2027 (Creely et al. 2007). The job-exposure matrix was, however, not designed to access exposures before the year 2000, and non-exposed job titles today might have been exposed in 1976–1983, causing misclassification with a weakening of the 1976–1983 findings. The observed associations in both cohorts could be due to unmeasured confounding unequally distributed between smoking status and exposure group. Occupationally exposed individuals may also have been exposed to traffic pollution and passive smoking. However, all individuals lived in Copenhagen, which minimizes possible differences in air pollution. We were not able to control for passive smoking. Yet, our main findings were related to the group of current smokers in whom secondhand smoking plays a less important role than in non-smokers. Chronic productive cough is correlated with gastroesophageal reflux syndrome and rhinosinus disease (Caminha et al. 2018; Hakansson et al. 2013; Ingebrigtsen et al. 2015), both independently associated with smoking. Yet, it is not likely that the extent of these differ between exposed and non-exposed. In our study, the odds ratio of chronic productive cough was slightly higher in former smokers than in never smokers, similar to prior findings (Brown et al. 1991; Lange et al. 1990a).

Self-reported asthma was more frequently reported in 2003–2017 reflecting an overall increase in the prevalence of asthma (Browatzki et al. 2009; Sears 2014). Asthma and airflow limitation ($FEV_1/FVC < 0.70$, which was our proxy for chronic obstructive lung disease) were both positively associated with a chronic productive cough but adjusting for or stratifying by these variables gave similar results. Also, we did not find any interactions of asthma or airflow limitation with occupational inhalant exposure on risk of chronic productive cough. Consequently, we did not consider asthma or FEV_1/FVC to be important mediators, confounders or effect modifiers.

All statistically significant main findings were within the range of odds ratios of 1.2 and 1.7. In comparison, being a light smoker increased the odds ratio of chronic productive cough to approximately 3, and heavy smoking to 10–13 (results not shown). Despite the different magnitudes of associations, chronic productive cough as a result of occupational exposures is important to detect and subsequently prevent. In some countries, regular lung function testing is mandatory in workers exposed to selected inhalant hazards (Hochgatterer et al. 2013). The standard test is spirometry, which is highly dependent on both the patient and the examiner, and even when conducted correctly, it is relatively insensitive to detect short-term differences (Hnizdo et al. 2006; Townsend 2000). Furthermore, a more rapid decline in lung function is not an obligate finding in all lung diseases, in particular not in asthma. Surveillance of new-onset chronic productive cough in exposed jobs might be an alternative. It is difficult to distinguish between chronic productive cough caused by cigarette smoking combined with occupational inhalant exposure as opposed to cigarette smoking alone. Nonetheless, chronic productive cough is associated with permanent lung damage such as accelerated lung function decline (Vestbo et al. 1996) and might pose a warning.

Strengths of our study include the large samples of randomly selected individuals separated in time, enabled assessment of period effects. The research question was not known to the participants, thereby minimizing over-reporting of the outcome by potentially concerned, exposed workers. Exposure was not self-reported, reducing the risk of recall and reporting bias. A proportion of our population had repeated measurements enabling generalized estimating equation , taking account of the correlation between successive measurements on the same individual.

The study has limitations. The use of a job-exposure matrix causes misclassification also in the contemporary cohort. The traditional way of assessing occupational inhalant exposure is personal or area sampling of specific substances, but such information is sparse and generally restricted to high-risk occupations. Job exposure matrices do not reflect the variation in exposure levels within a given occupation and person. Therefore, studies based upon JEMs will provide risk estimates for a narrower range of exposures

than studies based on individual assessments. However, risk estimates characterizing the actual contrast may not be biased depending on the type of error (Armstrong 1998).

Data on job titles were not complete from the DOC*X database and improved with time. In the 1980′ies, around 20% of the participants had missing job titles either due to unemployment, early retirement or lacking job titles from registers, and these individuals were excluded from all analyses. Temporality is a concern since our design did not ensure that exposure preceded the outcome. Unfortunately, data were not available to perform prospective data analysis. We did not know when participants started or stopped coughing, which did not allow us to study the influence from entering or exiting jobs with occupational inhalant exposures. In addition, individuals might change careers where the risk of exposure to inhaled pollutants is lower, i.e. adjustment to enable continued working. We were not able to identify the participants who experienced chronic productive cough secondary to other factors such as gastroesophageal reflux or rhinosinusitis. The exposed workers in this cohort generally derived from a lower socio-economic status than the unexposed group. To reduce the risk of bias, we controlled for the longest obtained education. The FEV_1/FVC ratio was based on spirometry performed at different time periods and with different equipment. Direct comparison was not possible as the spirometers stopped functioning. Any differences were, however, assumed to affect the unexposed and exposed individuals equally and were within the Copenhagen City Heart Study estimated to be minor (Lokke et al. 2013). Our population was predominantly middle-aged, and the results cannot without caution be extrapolated to younger age groups. Individuals returning to a cohort study are generally healthier than those who do not. The individuals of our study, with only one observation, were primarily part of the cohort still enrolling participants, and many of them had not yet been invited to a follow-up visit. The differences might, therefore, not be as large as could be expected. Baseline exposure, baseline chronic productive cough and baseline FEV_1/FVC did not differ between individuals with multiple visits and those individuals who only participated once in our studies.

In conclusion, selected occupational inhalant exposures were associated with chronic productive cough in two cohorts of the general population. Whereas this association was observed in both smokers and non-smokers in a 1976–83 cohort, it was only apparent in smokers in the 2003–2017 cohort.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval The cohort studies were approved by Danish Ethical Committees (KF-01-144/01, H-KF-01-144/01).

Consent to participate The cohort studies were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

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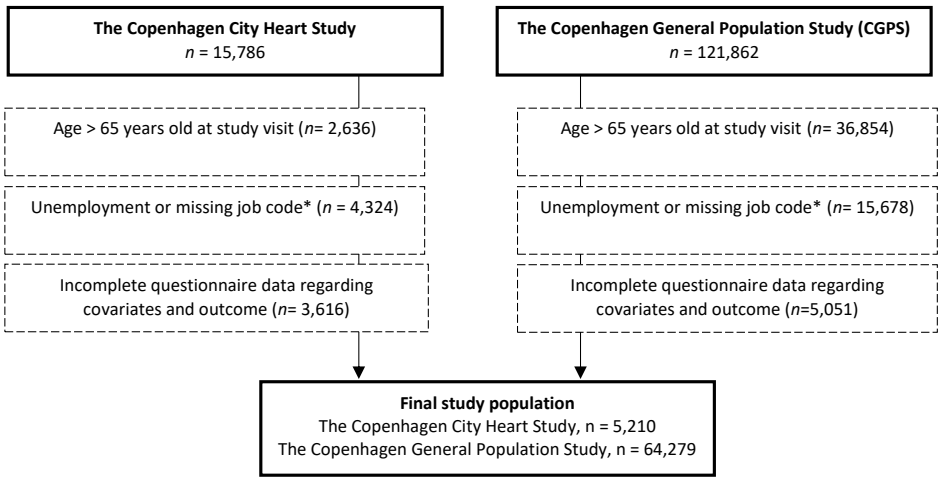
Supplementary Appendix

Chronic productive cough and inhalant occupational exposure – a study of the general population



Supplementary Figure 1

Flowchart of the study population from The Copenhagen City Heart Study (1976-1983) and The Copenhagen General Population Study (2003 – 2017). * Unemployment or missing job code one year prior to study visit.

Table S1. Fully adjusted model with odds ratios of chronic productive cough and exposure to vapours, gases, dusts or fumes from 1976-1983

	Non-smokers	**Smokers**
	Odds ratio (95% CI)	Odds ratio (95% CI)
Vapours, gases, dusts or fumes		
No	REF	REF
Low	1.2 (0.8;1.7)	0.9 (0.8;1.1)
High	**1.5 (1.0;2.3)**	**1.3 (1.1;1.6)**
Female sex	1.0 (0.7;1.3)	**0.8 (0.7;0.9)**
Age > 50 years old	**1.4 (1.0;2.0)**	**1.3 (1.1;1.5)**
BMI (kg/m^2)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
Smoking status		
Never	REF	-
Former	**1.4 (1.0:1.9)**	-
Light smoker	-	REF
Moderate smoker	-	**1.7 (1.4;1.8)**
Heavy smoker	-	**2.6 (2.1;3.1)**
Education		
Elementary	REF	REF
High school	1.0 (0.7;1.4)	0.9 (0.8;1.1)
Academic	1.5 (0.8;2.8)	0.9 (0.6;1.3)

Abbreviations: CI= Confidence Interval; REF = Reference: BMI = Body Mass Index.

Table S2. Fully adjusted model with odds ratios of chronic productive cough and exposure to vapours, gases, dusts or fumes from 2003-2017

	Non-smokers	**Smokers**
	Odds ratio (95% CI)	Odds ratio (95% CI)
Vapours, gases, dusts or fumes		
No	REF	REF
Low	1.0 (0.9;1.1)	**1.1 (1.0;1.3)**
High	1.0 (0.8;1.1)	**1.3 (1.1;1.5)**
Female sex	**0.8 (0.7;0.9)**	0.9 (0.9;1.1)
Age > 50 years old	**1.2 (1.1;1.4)**	**1.2 (1.1;1.4)**
BMI (kg/m^2)	**1.1 (1.0;1.1)**	1.0 (1.0;1.0)
Smoking status		
Never	REF	-
Former	**1.2 (1.1;1.3)**	-
Light smoker	-	REF
Moderate smoker	-	**2.2 (2.0;2.5)**
Heavy smoker	-	**4.3 (3.7;5.1)**
Education		
Elementary	REF	REF
High school	**0.7 (0.6;0.7)**	1.0 (0.9;1.1)
Academic	**0.6 (0.5;0.7)**	0.9 (0.8;1.1)

Abbreviations: CI= Confidence Interval; REF = Reference: BMI = Body Mass Index

Table S3. Odds ratios for chronic productive cough in exposed individuals with more than one study visit according to baseline smoking status and study period

	Period 1		**Period 2**	
	Non-smokers	Smokers	Non-smokers	Smokers
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Vapours, gases, dusts or fumes				
Low levels	1.0 (06;1.9)	0.9 (0.6;1.1)	1.0 (0.9;1.1)	1.0 (0.7;1.4)
High levels	**2.1 (1.1;4.0)**	1.3 (0.9;1.7)	1.0 (0.8;1.1)	1.1 (0.8;1.4)
Mineral dust				
Low levels	1.7 (0.9;3.4)	1.2 (0.9;1.7)	1.0 (0.8;1.1)	0.8 (0.6;1.3)
High levels	**2.0 (1.0:4.1)**	**1.9 (1.4;2.7)**	1.1 (0.9;1.3)	NA
Biological dust				
Low levels	0.9 (0.4;2.0)	0.9 (0.6;1.0)	0.9 (0.8;1.1)	1.2 (0.8;1.7)
High levels	**2.6 (1.0;6.7)**	1.0 (0.7;1.3)	1.2 (0.8;1.6)	NA
Gases and fumes				
Low levels	0.5 (0.2;1.5)	0.9 (0.6;1.4)	0.9 (0.7;1.1)	1.3 (0.8;2.1)
High levels	0.7 (0.2;3.2)	**2.0 (1.3;3.2)**	1.1 (0.9;1.4)	NA

Generalized estimating equations on longitudinal data only. All estimates are adjusted for age, sex, body mass index, and educational level, and additionally for smoking status (never or former smoker) in non-smokers and daily tobacco consumption in smokers (light, moderate, heavy smokers).

Occupational inhalant exposures and longitudinal lung function decline

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Abstract

Background Airborne exposures at the workplace are believed to be associated with lung function decline. However, longitudinal studies are few, and results are conflicting.

Methods Participants from two general population-based cohorts, the Copenhagen City Heart Study and the Copenhagen General Population Study, with at least two lung function measurements were followed for a mean of 9 years, range 3-27 years. Occupational exposure was assigned to each year of follow-up between two lung function measurement by a job exposure matrix. Associations between mean occupational exposure per year and mean annual decline in forced expiratory volume in 1 second (FEV_1) were investigated using linear mixed effects models according to cohort and time period (1976-1990 and 2003-2015). We adjusted for sex, height, weight, education, baseline FEV_1, and pack-years of smoking per year during follow-up.

Results A total of 16,144 individuals were included (mean age 48 years and 43% male). Occupational exposure to mineral dusts, biological dusts, gases & fumes, and a composite category were not associated with FEV_1 decline in analyses with dichotomized exposure. In analyses with an indexed measure of exposure, gases & fumes were associated with a FEV_1 change of -5.8 mL/unit/year (95% confidence interval:-10.8; -2.3) during 1976-1990, but not during 2001-2015.

Conclusion In two cohorts from the Danish general population, occupational exposure to dusts, gases, and fumes was not associated with excess lung function decline in recent years but might have been of importance decades ago.

Introduction

Lung function peaks in the twenties, and naturally declines with increasing age hereafter [1]. Tobacco smoking is the most important risk factor for accelerated lung function decline, which may lead to chronic obstructive pulmonary disease (COPD) [2]. In addition to smoking, occupational airborne exposures have been associated with lung function decline and COPD [3, 4]. The population attributable fraction of COPD due to occupational exposure has been estimated to be 15-20% [5]. Prior studies have mostly focused on high risk occupations such as coal mining [6, 7], welding [8, 9] and wood processing [10, 11]. Studies examining the association between ongoing exposure and change in lung function in the general population are few and inconclusive [12-20]. A recent study based on data from the Framingham Heart Study found an excess decline in forced expiratory volume in the first second (FEV_1) of 4.5 mL/year in "more likely dust exposed" individuals [14]. Another study based on two general population studies reported an excess decline of 0.6-0.8 mL/year for low and 2-3 mL/year for high exposure of biological and mineral dusts and metals [20]. A third study showed no excess decline in workers exposed to vapours, gases, dusts, and fumes, unless concomitant exposure to pesticides was present [12]. Discrepancies between the estimated impact of occupational airborne exposures and actual findings call for further exploration.

Accounting for occupational exposure in the period between two lung function measurements as an indication of ongoing rather than delayed health effects like tobacco smoking may be crucial [21, 22]. However, prior general population studies on occupational exposure and lung function decline have relied on a single or a few selected jobs held during follow-up [12-15], occupation at study entry [16, 17], or self-reported exposure either at baseline [18] or at the final examination [19].

In the present study, we investigated the association between occupational airborne exposure and longitudinal change in lung function, expressed as annual decline in FEV_1 in two population-based cohort studies from Denmark.

Methods

Study design

Individuals were recruited from two large Danish prospective population-based cohorts [23-25]: the Copenhagen City Heart Study and the Copenhagen General Population Study. The Copenhagen City Heart Study was initiated in 1976 and enrolled 19,825 individuals with subsequent follow-up examinations in 1981–83, 2001–03, and 2011–15. The Copenhagen General Population Study was initiated in 2003, is ongoing, and 109,538 individuals were included in this study. A follow-up examination was initiated from 2014, which now includes 29,884 [26]. Individuals in both cohorts were aged 20 years or older. All participants completed a questionnaire and a physical health examination including spirometry at each visit.

We included individuals with lung function measurements at two or more time points (supplementary figure 1). To examine a working population in an age group where lung function is thought to decline in a linear fashion [27], we excluded participants younger than 35 years of age at first lung function measurement and older than 65 at follow-up. Individuals with no employment in the follow-up period or with missing information on smoking habits or education were also excluded. None of the participants appeared in more than one of the cohorts. The cohort studies were approved by the Danish Ethical Committees and were carried out according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Lung function

Pre-bronchodilator FEV_1 and forced vital capacity (FVC) were measured in a standing position and repeated at least three times at each study visit. The test was accepted when the visual appearance of the spirometry tracing was within acceptable range, and at least two tests from a single visit did not differ more

than 5%. The highest values of FEV_1 and FVC were recorded. Three spirometers were used in the Copenhagen City Heart Study: Monaghan M-403 Spirometer (Monaghan, Littleton, Colorado, USA) from 1976-83, Vitalograph Spirometer (Maids Moreton, Buckinghamshire, UK) from 1991-03, and EasyOne Spirometer (ndd Medical Technologies, Zurich, Switzerland) from 2011-2015. In the Copenhagen General Population Study, Vitalograph Spirometer was used in the first 14,625 participants, and EasyOne Spirometer in the remainder of participants. Spirometers were replaced when they stopped functioning, and thereby a direct comparison was not possible; however, measurements from the Vitalograph and the EasyOne Spirometers have previously been compared with no major systematic differences of importance to the present study [28, 29].

Occupational exposure

Data on occupational airborne exposure was obtained through several steps. Every Danish citizen has a unique identification number since birth or immigration (the Civil Registration number) recorded in the national Danish Civil Registration System. The national Danish Civil Registration System was combined with the Danish Occupational Cohort (DOC*X) [30] to obtain complete job histories during the follow-up periods. Data included annual employment status (employed/not employed) and job codes according to the Danish version of the International Standard Classification of Occupation (DISCO-88). When a job code was missing, information from the most recent year was imputed (corresponding to 7% of all person-years). The Airborne Chemical Job Exposure Matrix (ACE JEM) [31] assigned occupational airborne exposure to each job code based on expert judgement. ACE JEM was developed for the UK SOC 2000 classification and was converted to DISCO-88 codes. if major and sub-major group codes in the DISCO-88 lacked SOC 2000 codes we generated exposure values by calculating the population distribution of the corresponding DISCO-88-unit groups. The following main categories of airborne agents were considered: mineral dust, biological dust, gases & fumes, and the composite category vapours, gases, dusts, or fumes (VGDF). The ACE JEM

dichotomized exposure into exposed and unexposed with additional information on level of exposure: not exposed, low (5-19 % of UK workplace limit), medium (20-49 % of UK workplace limit) and high exposure (≥50 % of UK workplace limit) as well as proportion of exposed individuals (<5%, 5-19%, 20-49%, and 50-100%). We constructed an indexed measure of exposure for each job by multiplying levels of exposure and proportion of exposed workers (supplementary table s1). Exposure was expressed ranging from 0 units (unexposed) to 2.5 units (a level of ≥50 % of the UK workplace limit and more than 50% of all workers exposed) (supplementary table s2). As the ACE JEM only reflected working conditions in the UK from 2000-2013 with no time-axis, we conducted separate analyses for the first years of the Copenhagen City Heart Study from 1976-1990.

Statistical analysis

We studied the association between occupational airborne exposure and change in FEV_1 using linear mixed-effects models with unstructured covariance [32]. In main analyses, the proportion of exposed years during follow-up was calculated by dividing the number of exposed years during a follow-up period by the total number of years. In subsequent analyses, mean units of indexed exposure per year was estimated by summing the units of exposure values for each year of follow-up divided by the total number of years. The outcome was expressed as mean annual change in FEV_1 and calculated for each follow-up period as the difference between the latter and the first of two sequential lung function measurements divided by number of years separating them. A fixed set of a priory explanatory variables were selected, that is, sex, and baseline height (cm), weight (kg), smoking (mean annual pack-years in the follow-up period), educational level (elementary, high school, academic), and FEV_1 (L). We assumed that FEV_1 decline in the included age group was linear and therefore did not adjust for age. Interaction of occupational exposure on smoking (mean pack-years) and sex was investigated. Each cohort was analyzed separately.

Supplementary analyses included males only, never-smokers only, and annual percentage change in FEV_1/FVC as an alternative outcome. To indicate whether the association between occupational exposure on lung function change varied over time, a secondary analysis was performed with data from the first two rounds of the Copenhagen City Heart Study (1976–78 and 1981–83) as opposed to later years (2001-2015). Excluded participants from the Copenhagen City Heart Study aged 35-65 years were characterized. We were not able to perform the analyses on excluded participants from the Copenhagen General Population Study, as the second round was not yet completed. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, USA).

Results

In total, 16,144 individuals were included (supplementary figure 1). Mean age at study inclusion was 48 years, and 61% in the Copenhagen City Heart Study were smokers at baseline as opposed to 20% in the Copenhagen General Population Study. Other characteristics are summarized in table 1. Follow-up time ranged from 3 to 27 years with a mean of 9 years. All participants from the Copenhagen General Population Study and the majority from the Copenhagen City Heart Study contributed with a baseline and a single follow-up visit, while 563 contributed with three lung function measurements. DISCO-88 codes were complete with all four digits in 66% of all employed years, whereas 4%, 1%, and 29% were only available at first, second and third level, respectively.

Table 1. Baseline characteristics according to cohort

	CCHS (n=8,202)	CGPS (n=7,942)	Total (n=16,144)
Age in years, mean (SD)	48 (7)	47 (5)	48 (6)
Male, n (%)	3,763 (46)	3,231 (41)	6,994 (43)
Smoking history, n (%)			
Never	1,711 (21)	3,554 (45)	5,265 (33)
Former	1,509 (18)	2,765 (35)	4,274 (26)
Current	4,982 (61)	1,623 (20)	6,605 (41)
Education, n (%)			
Academic	543 (7)	1,939 (24)	2,485 (15)
High school	2,629 (32)	5,268 (66)	7,897 (49)
Elementary	5,027 (61)	735 (9)	5,762 (36)
Height in cm, mean (SD)	169 (9)	173 (9)	171 (9)
Weight in kg, mean (SD)	72 (14)	76 (15)	74 (15)
FEV_1, in L, mean (SD)	2.9 (0.8)	3.3 (0.8)	3.1 (0.8)
FEV_1 %, mean (SD)	87 (16)	96 (13)	91 (16)
FEV_1/FVC, mean (SD)	0.80 (0.10)	0.80 (0.10)	0.80 (0.10)

Abbreviations: CCHS = The Copenhagen City Heart Study. CGPS = The Copenhagen General Population Study. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. FEV_1 % = FEV_1 % of predicted value.

Table 2 shows the distribution of follow-up years according to type of exposure during different time periods. The proportion of exposed years was relatively constant in all exposure categories. Overall results are presented in table 3, and the fully adjusted model in supplementary table s3. Mineral dust, biological dust, gases & fumes, and VGDF were not associated with change in FEV_1. In contrast, smoking one pack-year/year (corresponding to 20 cigarettes a day) was associated with change in FEV_1 of -17 mL/year (95% confidence interval [CI]: -19;-15) (table s3).

Table 2. Distribution of follow-up years according to occupational airborne exposure and calendar period

	< 1980 years (%)	**1980-1989** years (%)	**1990-1999** years (%)	**≥ 2000** years (%)
Vapours, gases, dusts, or fumes				
No exposure	14,489 (64)	18,684 (71)	6,818 (76)	73,321 (70)
Exposure	8,097 (36)	5,578(29)	2,152 (24)	31,304 (30)
Mineral dust				
No exposure	17,850 (79)	21,932 (83)	7,647 (85)	84,270 (81)
Exposure	4,736 (21)	4,530 (17)	1,323 (15)	20,355 (20)
Biological dust				
No exposure	20,855 (92)	24,616 (93)	8,315 (93)	90,241 (86)
Exposure	1,731 (8)	1,846 (7)	655 (7)	14,384 (14)
Gases & fumes				
No exposure	20,426 (90)	23,835 (90)	8,259 (92)	97,308 (93)
Exposure	2,160 (10)	2,627 (10)	711(8)	7,317 (7)

Years of unemployment not included in the number of follow-up years

Table 3. Mixed model of change in FEV_1 per dichotomized exposed year

	Change in FEV_1, mL/year (95% CI)			
	Copenhagen City Heart Study 1976-2013		**Copenhagen General Population Study 2003-2015**	
	Crude*	Adjusted**	Crude*	Adjusted**
Vapours, gases, dusts, or fumes	-2.9 (-6.4;0.6)	-2,0 (-5.3;1.3)	0.1 (-1.6;1.8)	0.7 (-0.9;2.3)
Mineral dusts	-3.8 (-8.0;0.4)	-2.1 (-6.0;1.8)	0.1 (-1.8;2.1)	0.8 (-1.0;2.7)
Biological dusts	3.7 (-2.2;9.5)	2.8 (-2.7;8.3)	0.1 (-2.1:2.3)	0.5 (-1.7;2.6)
Gases & fumes	-7.6 (-14.0;1.7)	-5.3 (-10.9;0.2)	1.3 (-1.8;4.5)	1.1 (-2.0;4.1)

A negative estimate denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Estimates adjusted for *sex and height **sex, height, weight, smoking (pack-years) per of follow-up year, baseline FEV_1, and education.

In analyses exploring differences between the two included cohorts and time periods using the indexed exposure measure, gases & fumes were associated with a change in FEV_1 of -5.8 mL/year (95% CI: -10.8;-2.3) per exposed unit in the Copenhagen City Heart Study, but not in the Copenhagen General Population Study (table 4). In stratified analyses, the association was only seen in early years of the study period (1976-1990) and not in later years. No associations were observed between mean dichotomized or indexed exposure and % FEV_1/FVC per year (supplementary tables S4 and S5). Analyses restricted to men or never-

smokers showed similar results without evidence of association between occupational airborne exposure and lung function decline. We found no interactions between occupational exposure and smoking or sex.

Table 4. Mixed model of change in FEV_1 per indexed exposed year

	Change in FEV_1, mL/ unit/year (95% CI)			
	Copenhagen City Heart Study		**Copenhagen General Population Study**	
	Crude*	Adjusted**	Crude*	Adjusted**
Vapours, gases, dusts, or fumes	-1.0 (-4.2;2.2)	-0.3 (-3.2;2.8)	0.5 (-1.1;2.0)	0.7 (-0.8;2.3)
Mineral dusts	-1.4 (-5.2;2.3)	-0.4 (-4.0;3.0)	0.2 (1.6;1.9)	0.4 (-1.3;2.1)
Biological dusts	1.7 (-9.6;12.9)	3.5 (-7.0;13.9)	1.1 (-3.3;5.5)	1.2 (-2.9;5.5)
Gases & fumes	**-5.6 (-11.0;-0.3)**	**-5.8 (-10.8;-2.3)**	0.7 (-2.4;3.8)	0.7 (-2.2;3.8)

A negative coefficient denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Unit range: 0 - 2.5 per year. Estimates adjusted for *sex and height **sex, height, weight, pack years per of follow-up year, baseline FEV_1 and education.

Discussion

In two longitudinal population-based cohort studies including 16,144 participants, we found that occupational exposure in the follow-up period to mineral dust, biological dust, gases & fumes, and VGDF were not associated with accelerated lung function decline from 2003-2015. However, exposure to gases & fumes four decades ago was associated with an excess annual FEV_1 decline.

Previous longitudinal general population studies of lung function decline are highly heterogenic and show small associations with airborne occupational agents [12, 14, 18, 20], a greater decline with exposure to an increasing number of agents [19], or no associations at all [13]. The studies rely mostly on self-reported job history or exposures obtained once, assess exposure differently, or differ in study populations which may explain the discrepancies. The most recent longitudinal general population study with similar exposure assessment, ages of participants and a long follow-up, concluded that one year of low exposure to mineral dust, biological dust, or metals was associated with 0.6-0.7 mL lower FEV_1, and one year of high exposure with 2-3 mL lower FEV_1 [20]. Nine other categories of exposure, including gases & fumes and VGDF were

not associated with lower FEV_1. The participants were selected from 38 out of 55 sites located in 23 countries, possibly with different working conditions than in Denmark. Importantly, the study reported that 25 pack-years of smoking were associated with a statistically insignificant decrease in FEV_1 of 11 mL corresponding to 0.4 mL per pack-year. This is inconsistent with both our findings and previous studies showing a mean difference of height-adjusted FEV_1 of 300-400 mL following 25 pack-years [33] or a decrease in FEV_1 of 6-11 mL per pack-year [34, 35].

A meta-analysis based on five longitudinal studies from 1987 to 2003 on occupational exposure to mineral dust found an excess decline in FEV_1 of 1.6 mL per 1 unit ($mg \cdot m^{-3} \cdot$ years) of respirable mineral dust [36]. The most prevalent high mineral dust exposed job in our population was construction workers. The geometric mean of respirable dust among indoor demolition workers in Denmark from 2012-2014 has been measured to 1 mg/m^3[37]. A theoretical excess decline in FEV_1 of 1-2 mL per year in exposed individuals would be difficult to demonstrate in our study setup, and the clinical relevance may be questionable.

Our study had several strengths. Job history was quite accurate within the follow-up periods, and we calculated average exposure during follow-up equivalent to cumulative exposure during follow-up, as length of follow-up periods were Indirectly factored into the analyses. Other strengths were repeated lung function measurements and the long follow-up time minimizing the within-person variation of FEV_1 [2].

Other general population-based studies with repeated lung function measurements have mostly relied on self-reported exposure or job history [12-16, 18, 19, 38] with risk of misclassification due to recall bias. Small effects caused by past exposures may be difficult to show. Some industry-based studies might be confounded by the healthy-worker effect, if individuals suffering from problems caused by or associated with the job, quit and are more likely to be lost to follow-up. In our cohort, job change did not directly affect participation.

Occupational history was based on data from the DOC*X database, and we carried prior occupation forward in years of employment, where job titles were missing with the risk of misclassification. Exposure

was estimated based upon JEM. This approach has strengths as well as some limitations. The JEM was based upon expert judgements by experienced occupational exposure assessors, but rigorous validation studies using workplace measurements as gold standard are not available. JEM tends to reduce degree of recall bias and hence differential misclassification as opposed to self-reported exposure. However, since JEM may not capture how exposure varies between workers within the same occupation, it may lead to non-differential misclassification.

We only included participants with two or more lung function measurements. Positive selection, i.e. that healthier subjects choose the most exposed jobs, has previously been shown [17]. Excluded subjects from the Copenhagen City Heart Study of the same age group as participants did however not differ significantly regarding exposure (results not shown). We did not exclude participants with lung disorders at baseline, as this could worsen the selection bias towards healthier individuals.

We studied the association of ongoing occupational exposure on decline in FEV_1 and disregarded prior exposure. It is possible that the effect of airborne exposure is time-dependent: either more harmful at the beginning or following many years of exposure. The response could also be delayed. We were not able to address this in our study. Although studies of the time effect of specific exposures on lung function are emerging [10], much is still unknown. However, if the effects of occupational exposure on FEV_1 resemble cigarette smoking, we would expect that the primary effect occurs concurrently with exposure.

As our study population was limited to European whites, aged 35 to 65 years old in an urban setting, our results cannot be generalized to other groups without caution. We used educational level as a proxy for socioeconomic status. Background and upbringing (i.e. passive smoking, living conditions, medical treatment of diseases), however, vary across social classes with the risk of residual confounding. Furthermore, jobs with exposure to airborne agents are primarily held by people in the lower social classes, which may confound the results.

Our results suggest that none of the selected airborne occupational exposures are currently associated with an excess decline in FEV_1 and consequently do not lead to an increased risk of developing COPD. However, exposure to gases & fumes in the early study period was associated with decline in FEV_1. As most airborne occupational exposures have declined substantially since the 1970ies [39], this is plausible. JEM assigned exposure to gases & fumes is highly correlated with exposure to mineral dust, and in 81% of all gases & fumes exposed years, exposure to mineral dust was also present. We did not have enough statistical power to conduct exposure interaction analyses, and results are most likely carried by a joint effect.

In conclusion, we found no associations between exposure to mineral dust, biological dust or gases & fumes and accelerated lung function decline in recent years.

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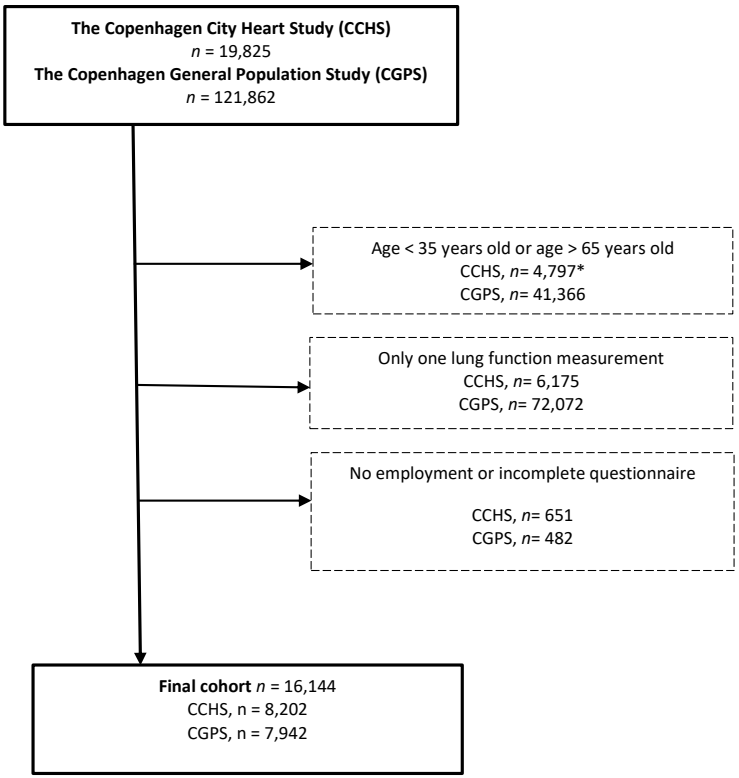
Supplementary Data



Supplementary Figure 1
Flowchart of the study population with at least two lung function measurements, aged 35-65 years old at baseline and follow-ups, *study visits in CCHS from 1991-1994 excluded **employed for at least one year during follow-up, with complete questionnaire data regarding smoking parameters and education.

Table S1. Principles for assigned values to the Airborne Chemical Job Exposure Matrix

	Category	Mean %	Assigned value
Level	Not exposed	0%	0
	Low (5-19 % of UK workplace limit)	12%	0.2
	Medium (20-49 % of UK workplace limit)	35%	0.5
	High (≥50 % of UK workplace limit)	75%	1
Proportion	0%	0%	0
	1-9%	5%	0.2
	10-50%	30%	1
	51-100%	75%	2.5

Table S2. Indexed exposure in the study population according to main category of exposure

		0 units	0.04-0.5 units	1-2 units	2.5 unit
CCHS	Vapours, gases, dusts or fumes	70%	23%	5%	3%
	Mineral dust	82%	12%	4%	2%
	Biological dust	91%	7%	1%	0%
	Gases & fumes	91%	5%	3%	1%
CGPS	Vapours, gases, dusts or fumes	70%	24%	3%	3%
	Mineral dust	80%	15%	2%	3%
	Biological dust	86%	12%	2%	0%
	Gases & fumes	93%	4%	3%	0%

Abbreviations: CCHS: The Copenhagen City Heart Study; CGPS: The Copenhagen City General Population Study. Numbers do not sum up to 100% due to rounding error.

Table S3. Change in FEV_1 per year in the fully adjusted model in The Copenhagen General Population Study

	Change in FEV_1 mL/year (95% CI)
Intercept	-12 (-30;7)
Vapours, gases, dusts or fumes (per exposed year)	0.7 (-0.9;2.3)
Female sex	-13 (-15;-11)
Smoking (pack-year/ year)	-17 (-19;-15)
Baseline FEV_1 (L)	-15 (-17;-14)
Education	
Elementary (ref)	Reference
High school	0.4 (-1.7;3.2)
Academic	0.7 (-1.7;2.7)
Height (cm)	0.3 (0.2;0.4)
Weight (kg)	0.01 (-0.04; 0.07)

A negative coefficient denotes a more rapid decline in FEV_1; a positive coefficient a less rapid decline. Abbreviations: FEV_1: forced expiratory volume in one second.

Table S4. Mixed model of FEV_1/FVC % change per year of dichotomized exposure

	Change in FEV_1/FVC % per year (95% CI)	
	The Copenhagen City Heart Study	The Copenhagen General Population Study
Vapors, gases, dusts and fumes	-0.1 (0.6;0.5)	-0.1 (-0,4;0.2)
Mineral dusts	-0.1 (-0.8;0.5)	0.01 (-0.3;0-3)
Biological dusts	-0.4 (-1.3;0.6)	-0.1 (-0.5;0.3)
Gases & fumes	0.5 (-0.5;1.4)	0.4 (-0.2;0.9)

A negative coefficient denotes a more rapid decline in FEV_1/FVC %; a positive coefficient a less rapid decline
Abbreviations: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Estimates adjusted for weight, height, sex, pack years per of follow-up year, baseline FEV_1 and education.

Table S5. Mixed model of FEV1/FVC % change per exposed year in indexed exposure

	Change in FEV_1/FVC % per year (95% CI)	
	The Copenhagen City Heart Study	The Copenhagen General Population Study
Vapors, gases, dusts and fumes	0.1 (-0.5;0.6)	0.1 (-0.2;0.3)
Mineral dusts	0.004 (-0.6;0.6)	0.2 (-0.1;0.5)
Biological dusts	0.8 (-1.0;2.6)	0.3 (-0.5;1.0)
Gases & fumes	0.4 (-0.5;1.2)	0.4 (-0.1;1.0)

A negative coefficient denotes a more rapid decline in FEV_1/FVC %; a positive coefficient a less rapid decline.
Abbreviations: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Estimates adjusted for weight, height, sex, pack years per of follow-up year, baseline FEV_1 and education.

PLOS ONE

RESEARCH ARTICLE

Occupational exposures and exacerbations of asthma and COPD—A general population study

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Abstract

Purpose

Recent studies suggest that occupational inhalant exposures trigger exacerbations of asthma and chronic obstructive pulmonary disease, but findings are conflicting.

Methods

We included 7,768 individuals with self-reported asthma (n = 3,215) and/or spirometric airflow limitation (forced expiratory volume in 1 second (FEV_1)/ forced expiratory volume (FVC) <0.70) (n = 5,275) who participated in The Copenhagen City Heart Study or The Copenhagen General Population Study from 2001–2016. Occupational exposure was assigned by linking job codes with job exposure matrices, and exacerbations were defined by register data on oral corticosteroid treatment, emergency care unit assessment or hospital admission. Associations between occupational inhalant exposure each year of follow-up and exacerbation were assessed by Cox regression with time varying exposure and age as the underlying time scale.

Results

Participants were followed for a median of 4.6 years (interquartile range, IQR 5.4), during which 870 exacerbations occurred. Exacerbations were not associated with any of the selected exposures (high molecular weight sensitizers, low molecular weight sensitizers,

Denmark: http://www.dst.dk/en/OmDS/organisation/. Data from the two cohorts, the Copenhagen City Heart Study and the Copenhagen General Population Study may be available for researchers who meet the criteria for access to confidential data. Contact information can be found at https://www.frederiksberghospital.dk/afdelinger-og-klinikker/oesterbroundersoegelsen/kontakt/Sider/default.aspx#10 and https://www.herlevhospital.dk/afdelinger-og-klinikker/klinisk-biokemisk-afdeling/forskning/Sider/Herlev-oesterbroundersoegelsen.aspx.

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irritants or low and high levels of mineral dust, biological dust, gases & fumes or the composite variable vapours, gases, dusts or fumes). Hazards ratios ranged from 0.8 (95% confidence interval: 0.7;1.0) to 1.2 (95% confidence interval: 0.9;1.7).

Conclusion

Exacerbations of obstructive airway disease were not associated with occupational inhalant exposures assigned by a job exposure matrix. Further studies with alternative exposure assessment are warranted.

Introduction

Globally, asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent and common causes of morbidity and mortality [1–3]. While airflow limitation and inflammation in asthma may resolve spontaneously or in response to medication, airway obstruction in COPD is, by definition, persistent. Asthma involves the large and small airways, whereas COPD is a disease primarily in the small airways. The two conditions are overlapping. Patients with asthma might develop chronic airway obstruction, and elements of reversible airflow limitation are often present in COPD [4–6].

Exacerbations are acute worsening of asthma or COPD and are often defined on the basis of management: treatment with oral corticosteroids and antibiotics in an outpatient setting (moderate exacerbations), or managed in emergency care with or without hospital admission (severe exacerbations) [7–9]. Exacerbations are associated with an accelerated loss of lung function among some asthmatic patients [10] and decreased survival in patients with COPD [11, 12]. Possible triggers of exacerbations of asthma and COPD include infections, low temperatures and exposure to different types of airborne particles [13, 14]. Airborne particles include ambient air pollution with well-described associations to exacerbations of COPD [15] and asthma [16–18], and occupational inhalant exposures with much less evident associations. Occupational studies have largely focused on new-onset asthma or COPD [19–22]. It is, however, possible that workplace hazards are associated with exacerbations of asthma and COPD, and that these may cause greater morbidity [23]. Exacerbations of both diseases might be associated with the same inhalant hazards at work but are rarely studied together. Recent studies suggest that different types of inhalant exposures in the workplace are associated with exacerbations of asthma [24] and COPD [25], but rely on self-reported exacerbations which are prone to recall bias. Updated information on the risk of exacerbations is important for evidence-based guidance of asthma and COPD patients in general.

We studied the association between concurrent inhalant occupational exposures and exacerbations of asthma and/or COPD.

Methods

Population

Participants were selected from two large cohort studies: The Copenhagen City Heart Study (CCHS) [26] and The Copenhagen General Population Study (CGPS) [27]. CCHS was initiated in 1976, and the fifth round of follow up was completed in 2015. CGPS started in 2003 and is a prospective cohort study with ongoing recruitment of participants. Individuals from the fourth (2001–2003) and/or the fifth (2011–2015) follow up round of CCHS and from

2003–2016 in the CGPS were eligible for the present study. Participants in both studies were 20–100 years old and had been randomly selected from the general population through the Danish Civil Registration Service. All participants gave written informed consent, and both studies were approved by the Danish Ethics Committees. All data were fully anonymized before assessment. At each round of examination, participants filled out a questionnaire, and completed a physical examination at a test center located at a public hospital in Copenhagen. The questionnaire was self-administered, concerning health status, lifestyle and socio-economic status, and was assessed by one of the investigators on the day of attendance. The physical examination included spirometry. Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured by investigators and repeated three times with the participant in a standing position. The test was redone if the two closest trials differed by more than 5%, or the visual appearance of the spirometry tracing was unsatisfactory. A Vitalograph spirometer (Maids Moreton, Buckinghamshire) was used in The Copenhagen City Heart Study and by the first 14,624 individuals in the Copenhagen General Population Study, while an EasyOne Diagnostic Spirometer (ndd Medizintechnik, Switzerland) measured lung function in the remaining individuals.

Individuals were included in the present study, if they reported asthma in the questionnaire and/or had spirometry indicating airflow limitation (FEV_1/ FVC < 0.70). Other inclusion criteria in the present study were age 30–60 years at baseline, employment at least one year during the study period, and complete data regarding smoking habits, education, weight, height and spirometry.

A sample of individuals with no reported asthma and with $FEV_1/FVC \geq 0.70$ was constructed to test for differences in baseline exposure. A one-to-three matching was conducted based on age at inclusion, sex, smoking status (never, former, current smoker), BMI category (<18.5, 18.5–24.9, 25–29.9, 30+ kg/m2), education (elementary, high school, academic) and participation after the year 2000.

Exposure

We combined job codes from the Danish Occupational Cohort database (DOC*X) [28] with job exposure matrices to determine exposure each year of the follow-up period (S1 Table). DOC*X is a database with annual job titles according to the Danish version of the International Standard Classification of Occupation (DISCO-88) on all Danish wage earners from 1970 until present. For the participants with complete job histories, exposure status was relatively stable during employed year of follow up. In case of missing job codes in employed years, prior job titles maximally five years prior were extrapolated. We applied parts of two expert-rated job exposure matrices; the Airborne Chemical Job Exposure Matrix (ACEJEM) [29] commonly used for chronic obstructive lung disease, and the Occupational Asthma-specific JEM (OAsJEM) [30] designed for occupational asthma. The ACE JEM was developed for the UK SOC 2000 classification job codes, the OAsJEM for the International Standard Classification of Occupation (ISCO-88), and both were converted into DISCO-88 codes. The ACE JEM included information on 12 pollutant types (including composites) and assigned proportion of exposed workers (<5%, 5–19%, 20–49%, ≥50%), level of exposure (not exposed, low, medium, high) and a binary variable (non-exposed, exposed) to each job code. The OAsJEM covered 30 different sensitizers or irritants, and each job code was classified in three categories: high ("at least 50% of the workers exposed and moderate to high intensity"), medium ("low to moderate probability or low intensity of exposure, such as 'high probability and low intensity' or 'low probability and moderate to high intensity'") and not exposed ("unlikely to be exposed with low probability and low intensity").

To achieve adequate power we selected the following main types of exposure: mineral dust, biological dust, gases & fumes and the composite variable of vapours, gases, dusts or fumes (VGDF) from the ACE JEM, and high molecular weight sensitizers, low molecular weight sensitizer and irritants from the OAsJEM. Probability and intensity of exposure assigned by the ACEJEM were combined into the following classes: no, low and high exposure (S2 Table). Exposure in the OAsJEM was dichotomized into exposed (including high and medium exposure assigned by the OAsJEM) and unexposed.

Outcome

Exacerbations were defined by treatment with oral corticosteroids, emergency care unit assessment (emergency care) or hospital admission related to asthma or COPD. Cases were identified through linkage with The Danish National Prescription Registry [31] and The Danish National Patient Register [32]. Treatment with oral corticosteroids included prescriptions for prednisolone (ATC code H02AB06) or prednisone (H02AB07). Emergency care or hospital admissions comprised of the following: (1) primary diagnosis "chronic obstructive pulmonary disease" (ICD-code J44) and secondary diagnosis "pneumonia" (J13 to J18) or (2) primary diagnosis "asthma" (J45) or "status asthmaticus" (J46) or (3) primary diagnosis "respiratory failure" (J96) in combination with a secondary diagnosis "chronic obstructive pulmonary disease" (J44) or "asthma" (J45) or "status asthmaticus" (J46). The highest level of treatment per episode was recorded, and the date of prescription, emergency care or hospital admission day denoted an event. Exacerbations one year prior to inclusion were recorded separately. In case of an exacerbation occurring before inclusion and less than four weeks before an event in the follow-up period, the event was regarded as an exacerbation in the previous year.

Covariates

Based upon status at inclusion, the following covariates were included; sex, smoking status (never, former, current smoker), BMI category ($<$18.5, 18.5–24.9, 25–29.9, 30+ kg/m^2), education (elementary, high school, academic), FEV_1% predicted class ($<$80% and $\geq$80%) and exacerbations one year prior to study inclusion (none, $\geq$1). Calculation of FEV_1% predicted has previously been described [33].

Statistics

In a follow-up design, we used Cox regression with time-varying exposure to examine the hazard ratio (HR) of exacerbation according to inhalant exposure. Age was the underlying time scale, and end of follow-up was the first occurring exacerbation, exit from the labour market, death or year 2017, whichever came first. We found no interactions between the effects of exposure and sex, exposure and smoking status, exposure and FEV_1% predicted or exposure and exacerbations one year prior to inclusion. Stratifying by exacerbation within the year before inclusion or excluding the covariate from the model did not change main findings. We conducted sensitivity analyses including only self-reported asthma, $FEV_1/FVC<0.70$ or individuals with a complete job history. To ensure temporality between exposure and outcome we repeated all analyses with inhalant exposure assigned the previous year of all follow-up years. Collinearity of exposures did not allow for analyses including more than one type of exposure in a model. Proportional hazards assumptions were evaluated graphically. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses. P-values were two-sided, and statistical significance was defined as $p<0.05$.

Results

A total of 7,768 individuals with self-reported asthma, $FEV_1/FVC<0.70$ or a combination of the two were included. The mean age at study inclusion was 50 years (standard deviation, SD 7), and 62% were current or former smokers (Table 1).

Exposure to the selected inhalant agents at study inclusion varied from 28% exposed to low levels of vapours, gases, dusts or fumes (VGDF) to 2% exposed to high levels of biological dust and gases & fumes (Table 2). At the time of study inclusion, 61% of the population (N = 4,736) was not exposed to any of the selected inhalant agents. Proportions of exposed in the matched population with no self-reported asthma and $FEV_1/FVC \geq 0.70$ resembled our population (S3 Table).

First time exacerbation since study inclusion was recorded in 870 individuals during a median of 4.6 years (interquartile range, IQR 5.4). The number of exacerbations was 411 among individuals with self-reported asthma only, 317 in the group of participants with $FEV_1/FVC < 0.70$ only, and 142 in the remaining participants. Only 8% of the exacerbations involved emergency care or hospital admission. Exacerbations were associated with low FEV_1 at inclusion; HR 1.5 (95% confidence interval [CI] 1.3;1.8), a body mass index above normal at

Table 1. Characteristics of the study population at inclusion.

	N = 7,768
Age, years, mean (SD)	50 (7)
Sex, male, n(%)	
Male	3,361 (43)
Female	4,407 (57)
BMI, n(%)	
<18.5	54 (1)
18.5–24.9	3,716 (48)
25–29.9	2,869 (37)
≥30	1,129 (15)
Education, n(%)	
Elementary	672 (9)
High school	4,774 (61)
Academic	2,322 (30)
Smoking, n(%)	
Never smoker	2,984 (38)
Former smoker	3,083 (40)
Current smoker	1,701 (22)
Self-reported asthma, n(%)	3,215 (42)
$FEV_1/FVC < 0.70$, n(%)	5,275 (68)
Self-reported asthma and FEV1/FVC <0.70, n(%)	722 (9)
FEV_1% predicted, n(%)	
≥80%	5,806 (75)
<80%	1,962 (25)
Exacerbations one year prior to inclusion, n(%)	
No	7,562 (97)
≥ 1	206 (3)

Abbreviations; SD: standard deviation; n: number; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

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Table 2. Exposures at study inclusion.

	Exposure, number (row-%)		
	Unexposed	**Low**	**High**
ACE JEM			
Vapors, gases, dusts or fumes	4,906 (63)	2,184 (28)	678 (9)
Mineral dusts	6,167 (79)	1,189 (15)	412 (5)
Biological dusts	6,368 (82)	1,276 (16)	124 (2)
Gases&fumes	7,236 (93)	352 (5)	180 (2)
	Unexposed	**Exposed**	
OAsJEM			
High molecular weight sensitizer	6,739 (87)	1,029 (13)	
Low molecular weight sensitizer	6,633 (85)	1,135 (15)	
Irritants	5,889 (76)	1,879 (24)	

Abbreviations: ACE JEM: The Airborne Chemical Job Exposure Matrix; OAsJEM: The Occupational Asthma-specific JEM

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inclusion; HR for BMI 25–29.9: 1.3 (95% CI: 1.1;1.5); HR for BMI≥30: 1.5 (95% CI 1.3;1.9) and female sex; HR 1.5 (95% CI 1.3;1.8) (S4 Table). Having had an exacerbation in the year before inclusion (n = 206) was associated with a hazard ratio of 6.9 (95% CI 5.6;8.5) of a new exacerbation.

Main results are presented in Table 3. We found no associations between exacerbations and mineral dust, biological dust, gases & fumes, vapours, gases, dusts or fumes (VGDF), high molecular weight sensitizer (HMW), low molecular weight sensitizer (LMW) or irritants. Analyses on self-reported asthma only (S5 Table) or $FEV_1/FVC < 0.70$ (S6 Table) showed similar results except for exposure to low levels of gases & fumes which was associated with a hazard ratio of 1.6 (95% CI 1.1;2.3). Repeating the analyses with exposure assigned one year prior, excluding FEV_1% predicted as a covariate or only including individuals with a complete job history did not change our main findings.

Discussion

Our study is the first to comprehensively assess the association between exacerbations and inhalant occupational hazards in a large population of individuals from the general population with self-reported or spirometric measures indicating asthma or COPD. An exacerbation was recorded in 870 out of 7,768 individuals with self-reported asthma and/or airflow limitation during a median follow-up of 4.6 years (interquartile range, IQR 5.4). In line with findings from clinical cohorts of patients with asthma and COPD, the exacerbation risk was significantly higher in individuals with low lung function and a history of previous exacerbations. There was no association between occupational inhalant exposures and exacerbations. Including only individuals with self-reported asthma or participants with airflow limitation did not alter the results, apart from the observation that low levels of gases & fumes were associated with exacerbations in individuals with self-reported asthma.

The strong association between prior exacerbations and future events is well-established [34, 35]. In our population of individuals with self-reported asthma, 4% exacerbated within the first 12 months of follow-up, and 6% of these were defined by a hospital admission or emergency care. In line with this, a large study of patients with asthma with similar ages and access to health care who received at least one type of asthma medication reported that within 12 months 8% exacerbated and 16% of these required hospital admissions or emergency care in

Table 3. Associations between inhalant exposures and exacerbations.

	Exacerbations	Follow-up years	Crude	Adjusted*
	Number	*Number*	*HR (95% CI)*	*HR (95% CI)*
Vapors, gases, dusts or fumes				
No	553	26.340	1 (ref)	1 (ref)
Low	222	11.683	0.9 (0.8;1.1)	1.0 (0.8;1.1)
High	78	3.508	1.1 (0.9;1.4)	1.0 (0.8;1.3)
Mineral dusts				
No	692	33.244	1 (ref)	1 (ref)
Low	114	6.133	0.9(0.8;1.1)	1.0 (0.8;1.2)
High	47	2.154	1.1(0.8;1.4)	1.0 (0.7;1.3)
Biological dusts				
No	709	34.031	1 (ref)	1 (ref)
Low	132	6.841	0.9 (0.8;1.1)	0.9 (0.7;1.0)
High	12	660	0.9 (0.5;1.6)	0.8 (0.5;1.5)
Gases&fumes				
No	792	38.811	1 (ref)	1 (ref)
Low	42	1.706	1.1 (0.8;1.5)	1.2 (0.9;1.7)
High	19	1.015	1.0 (0.7;1.5)	0.9 (0.5;1.4)
High molecular weight sensitizer				
Unexposed	747	35.978	1 (ref)	1 (ref)
Exposed	106	5.554	0.9 (0.8;1.1)	0.8 (0.7;1.0)
Low molecular weight sensitizer				
Unexposed	723	35.619	1 (ref)	1 (ref)
Exposed	130	5.913	1.1 (0.9;1.3)	1.0 (0.8;1.2)
Irritants				
Unexposed	632	31.861	1 (ref)	1 (ref)
Exposed	221	9.671	**1.1 (1.0;1.3)**	1.0 (0.9;1.2)

Cox regression with time varying exposure and age as underlying time scale *Adjusted for sex, education, smoking status, body mass index and FEV_1% predicted. Abbreviations; HR: hazard ratio; CI: confidence interval.

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the UK [34]. A possible explanation for the slightly lower occurrence in our study is that our definition of asthma did not require the use of asthma medication thereby including milder and inactive cases.

Exacerbations of asthma and COPD have been studied separately in recent occupational studies, and results of one study are partly in agreement with our findings [24], whereas others are not [25, 36]. Consistent with our results, JEM assigned exposure to agents with high molecular weight, low molecular weight or irritating properties were not associated with exacerbations treated by oral corticosteroids or requiring emergency treatment or hospital admission [24]. Self-reported exposure to biological dust and the composite variable gas, smoke or dust but not mineral dust was, however, positively associated with exacerbations requiring emergency care treatment or hospital admission, but not to exacerbations controlled by corticosteroids alone. In another study, asthma exacerbations were associated with high and low levels of biological dust and high and not low levels of mineral dust, gases and fumes and a composite variable [36]. In a population of current or former smokers with COPD, intermediate/high risk of exposure in the longest-held job was associated with exacerbations requiring health care utilization with low risk of exposure as a reference [25].

The diverging results might overall be explained by different ways of assessing exacerbations and exposure or the chosen covariates. In all studies mentioned above, exacerbations were self-reported and thereby susceptible to recall bias. Exposure was accounted for differently; not required to be concurrent with exacerbations [25] or the reported significant findings were based on self-reports [24]. We adjusted for body mass index (BMI) and education as a proxy of socioeconomic position. Both have been shown to be directly or indirectly associated with exacerbations of asthma [37–39] and possibly correlated with occupational exposure. The two studies concerning exacerbations of asthma [24, 36] did not control for these which might contribute to the different findings.

Our results suggest that exposure to the selected inhalant hazards is not associated with exacerbations in individuals with airway obstruction who are able to continue to work. Improved technology and governmental regulation are important contributors to a large decrease in most occupational inhalant exposures since the 1970s [40] making findings plausible. Traditionally, asthma and COPD have not been studied together in the occupational setting. However, the diseases are overlapping and difficult to distinguish between solely based on data available in our cohorts. Even in studies with access to post-bronchodilator pulmonary function data, reversibility was found in 44–50% of patients with COPD [41, 42], and 25% of asthma patients aged 55 or older had a co-existent diagnosis of COPD [43]. In analyses restricting the population to self-reported asthmatics, we found that low levels of gases & fumes were associated with exacerbations with a hazard ratio of 1.6 (1.1;2.3). The finding might be explained by multiple testing, but is biologically plausible, as asthma exacerbations are also associated with outdoor ambient particulate matter [44]. Regardless, our finding needs to be replicated in other studies.

Strengths of the study included register-based job titles year by year, securing concurrent exposure. Exacerbations were identified in registers and not prone to recall bias. The population represented a wide range of the general population enabling analyses of exposed or unexposed individuals with the same educational level as a proxy of socioeconomic position. Exposure rates were comparable to a matched group of controls.

Our study has limitations. The population was selected by a self-reported diagnosis of asthma or spirometry indicating airflow limitation. A large proportion of individuals with FEV_1/FVC below 0.70 was never smokers in the present study. Some of these may have undiagnosed asthma. However, a study with post-bronchodilator spirometry reported similar findings among never smokers [45]. In total, 312 exacerbations occurred among individuals with $FEV_1/FVC<0.70$ and no self-reported asthma, and 24% (74/312) of these among never smokers suggesting that this group of individuals were indeed ill. Exposure was assigned by job exposure matrices (JEM), which inevitably causes misclassification, as JEMS do not account for variations in levels of exposure within jobs or at the individual level. However, if the mean exposure level for a given job is accurate, this misclassification is not likely to result in attenuated risk estimates, because the measurement error is of Berkson type [46]. We do acknowledge that validation studies for the applied JEMS are not available, and therefore non-differential misclassification towards zero cannot be ruled out. The occupational airborne chemical exposure matrix (ACE JEM) [29] and the occupational asthma-specific JEM (OAs-JEM) [30] were created with an emphasis on detecting new-onset asthma and COPD rather than exacerbations. The selected categories of exposure were, however, considered to be possible occupational triggers of exacerbations of COPD and asthma. We were not able to account for the use of respiratory protective equipment (RPE), as this was not included in the ACE JEM or in the questionnaire. Legislation in Europe introduced in the 1980s has focused on adjustment of use of RPE as well as assessing its effectiveness, and thus RPE is now considered a last resort of protection. Exacerbations were identified by prescription for oral

corticosteroids, which are also prescribed for other diseases such as rheumatoid arthritis and inflammatory bowel disease. Yet, the method has previously been validated and is generally accepted [47], and the risk of bias is considered non-differential. Finally, we did not control for ambient air pollution, as our population was urban. Our population was relatively young, and we did not adjust for comorbid disease. We did not have information on atopy, which may play a role in asthma exacerbations, but its role in late-onset asthma is considered small [48]. Our study population is not representative of all patients with airflow limitations. The mean age at inclusion was 50 years old, and the median follow-up time was 4.6 years. Traditionally, COPD was considered a disease of those aged >50 years, but is suggested to be detectable in 20–45 year old individuals [49]. Still, our population is young. As concomitant exposure was essential in our study, we did not include older participants. Only 9% of the participants reported elementary school as highest level of education. The corresponding rate in the general population aged 35–65 years old in the capital region of Denmark in 2008 was 21% [50] and 24% in the first round of examinations in The Copenhagen General Population Study. A possible explanation for the lower frequency in our population is that the overall lower employment rates among individuals with asthma and COPD are most pronounced in lower educational levels [51–53]. Consequently, power in the present study may be affected.

In conclusion, our results indicate that occupational exposures in Danish individuals who continue to work despite asthma and COPD are not associated with a higher risk of exacerbations.

Supporting information

S1 Table. Overview of the methodology.
(DOCX)

S2 Table. Exposure classes combining level and proportion of exposure assigned by the Airborne Chemical Job Exposure Matrix.
(DOCX)

S3 Table. Exposure at study inclusion in study population and matched group.
(DOCX)

S4 Table. Full Cox regression model with time varying exposure and age as underlying time scale.
(DOCX)

S5 Table. Associations between exposure and exacerbations of self-reported asthma.
(DOCX)

S6 Table. Associations between selected inhalant hazards and exacerbations in individuals with FEV1/FVC<0.70.
(DOCX)

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Table S1. Overview of the methodology

Step	Course of action
1	Cohort studies conducted
2	Study population selected based on inclusion and exclusion criteria
3	Job codes held during follow-up obtained from the Danish Occupational Cohort database (DOC*X)
4	Imputation of missing job codes
5	Conversion of job exposure matrices (the Airborne Chemical Job Exposure Matrix (ACEJEM) and the Occupational Asthma-specific Job Exposure Matrix (OAsJEM)) to Statistics Denmark's Classification of Occupations (DISCO-88)
6	Exposure classes established
7	Job codes linked with the job exposure matrices for selected categories of exposure
8	Outcome variables collected from The Danish National Prescription Registry and The Danish National Patient Register
9	Analyses conducted

Table S2. Exposure classes combining level and proportion of exposure assigned by The Airborne Chemical Job Exposure Matrix

		Proportion			
		<5%	5-19%	20-49%	≥50%
Level	Not exposed	Not exposed	Not exposed	Not exposed	Not exposed
	Low	Not exposed	Low	Low	Low
	Medium	Not exposed	Low	Low	High
	High	Not exposed	Low	Low	High

Table S3. Exposure at study inclusion in study population and matched group

	Study population			Matched* group of participants		
	Exposure, number (row-%)			Exposure, number (row-%)		
ACE JEM	Unexposed	Low	High	Unexposed	Low	High
Vapors, gases, dusts or fumes	4,906 (63)	2,184 (28)	678 (9)	15,143 (65)	6,271 (27)	1,851 (8)
Mineral dusts	6,167 (79)	1,189 (15)	412 (5)	18,731 (81)	3,420 (15)	1,114 (5)
Biological dusts	6,368 (82)	1,276 (16)	124 (2)	19,384 (83)	3,517 (15)	364 (2)
Gases&fumes	7,236 (93)	352 (5)	180 (2)	21,823 (94)	915 (4)	527 (2)
OAsJEM	Unexposed	Exposed		Unexposed	Exposed	
High molecular weight sensitizer	6,739 (87)	1,029 (13)	-	20,400 (88)	2,865 (12)	-
Low molecular weight sensitizer	6,633 (85)	1,135 (15)	-	19,981 (86)	3,284 (14)	-
Irritants	5,889 (76)	1,879 (24)	-	18,067 (78)	5,198 (22)	-

*One-to-three matched controls based on sex, age at inclusion, smoking status, BMI, education and participation after the year 2000. Abbreviations: ACE JEM: The Airborne Chemical Job Exposure Matrix; OAsJEM: The Occupational Asthma-specific JEM

Table S4. Full Cox regression model with time varying exposure and age as underlying time scale

	Hazard ratio (95% CI)
Vapours, gases, dusts or fumes	
No	1 (ref)
Low	1.0 (0.8;1.1)
High	1.0 (0.8;1.3)
Sex	
Male	1 (ref)
Female	**1.5 (1.3;1.8)**
Education*	
Elementary	1 (ref)
High School	0.9 (0.8;1.2)
Academic	0.8 (0.6;1.1)
Smoking*	
Never	1 (ref)
Former	1.1 (0.9;1.3)
Current	1.1 (0.9;1.4)
Body mass indexI*	
<18.5	1.2 (0.6;2.3)
18.5-24.9	1 (ref)
25-29.9	**1.3 (1.1;1.5)**
≥30	**1.5 (1.3;1.9)**
FEV_1 % predicted*	
≥80%	1 (ref)
<80%	**1.5 (1.3;1.8)**
Exacerbations one year prior to inclusion	
No	1 (ref)
≥ 1	**6.9 (5.6;8.5)**
* Status at baseline. Abbreviations; CI: confidence interval	

Table S5. Associations between exposure and exacerbations of self-reported asthma

	Events	**Crude**	**Adjusted***
	Number	***HR (95% CI)***	***HR (95% CI)***
Vapors, gases, dusts or fumes			
No	355	1 (ref)	1 (ref)
Low	136	0.9 (0.7;1.1)	0.9 (0.7;1.1)
High	50	**1.3 (1.0;1.7)**	1.0 (0.8;1.4)
Mineral dusts			
No	437	1 (ref)	1 (ref)
Low	74	0.9 (0.7;1.2)	1.0 (0.8;1.3)
High	30	1.3 (0.9;1.8)	1.0 (0.7;1.5)
Biological dusts			
No	449	1 (ref)	1 (ref)
Low	83	0.9 (0.8;1.2)	0.8 (0.7;1.1)
High	9	NA	NA
Gases&fumes			
No	499	1 (ref)	1 (ref)
Low	28	1.4 (0.9;2.0)	**1.6 (1.1;2.3)**
High	14	1.3 (0.8;2.2)	1.0 (0.6;1.6)
High molecular weight sensitizer			
Unexposed	476	1 (ref)	1 (ref)
Exposed	65	0.9 (0.7;1.2)	0.8 (0.6;1.0)
Low molecular weight sensitizer			
Unexposed	466	1 (ref)	1 (ref)
Exposed	75	1.0 (0.7;1.2)	0.9 (0.7;1.1)
Irritants			
Unexposed	409	1 (ref)	1 (ref)
Exposed	132	1.1 (0.9;1.4)	1.0 (0.8;1.2)

Cox regression with time varying exposure and age as underlying time scale *adjusted for sex, education, smoking status, body mass index and FEV_1 % predicted. Abbreviations; HR: hazard ratio; CI: confidence interval.

Table S6. Associations between selected inhalant hazards and exacerbations in individuals with $FEV_1/FVC<0.70$

	Events	**Crude**	**Adjusted***
	Number	***HR (95% CI)***	***HR (95% CI)***
Vapors, gases, dusts or fumes			
No	278	1 (ref)	1 (ref)
Low	123	1.0 (0.8;1.2)	1.0 (0.8;1.2)
High	51	1.3 (1.0;1.7)	1.1 (0.8;1.6)
Mineral dusts			
No	365	1 (ref)	1 (ref)
Low	56	0.9 (0.7;1.2)	0.9 (0.7;1.3)
High	31	1.2 (0.8;1.7)	1.1 (0.8;1.7)
Biological dusts			
No	368	1 (ref)	1 (ref)
Low	78	1.1 (0.8;1.4)	1.0 (0.8;1.3)
High	6	NA	NA
Gases&fumes			
No	418	1 (ref)	1 (ref)
Low	19	0.9 (0.6;1.4)	1.0 (0.6;1.6)
High	15	1.2 (0.7;2.0)	1.1 (0.7;1.9)
High molecular weight sensitizer			
Unexposed	390	1 (ref)	1 (ref)
Exposed	62	1.0 (0.8;1.3)	0.9 (0.7;1.2)
Low molecular weight sensitizer			
Unexposed	371	1 (ref)	1 (ref)
Exposed	81	**1.3 (1.0;1.7)**	1.3 (0.9;1.6)
Irritants			
Unexposed	317	1 (ref)	1 (ref)
Exposed	135	**1.3 (1.1;1.6)**	1.2 (0.9;1.5)

Cox regression with time varying exposure and age as underlying time scale *adjusted for sex, education, smoking status, body mass index and FEV_1 % predicted. Abbreviations; HR: hazard ratio; CI: confidence interval.