Slutrapport til Arbejdsmiljøforskningsfonden:

Forebyggelse af autoimmune sygdomme i hud, lunger, kar og led forårsaget af kvartseksponering i arbejdsmiljøet

Signe Hjuler Boudigaard, Jesper Medom Vestergaard, Klaus Søndergaard, Kjell Torén, Hans Kromhout, Karoline Kjærgaard Hansen, Vivi Schlünssen, Henrik Kolstad

DANSK ramazzini CENTER
forskning i miljø og arbejdsmedicin

midt regionmidtjylland

AARHUS UNIVERSITET

Indholdsfortegnelse

Resume

Kvarts findes naturligt i sand, sten, klipper og menneskabte materialer produceret herfra, som beton, mursten, tegl og keramiske produkter. Arbejdere indenfor bygge-anlæg, landbrug, mineraludvinding og fremstillingsindustri udsættes for fint kvartsstøv. Der er begrænset viden om aktuelle kvartseksponeringsniveauer i Danmark og ikke mindst, hvilke forhold der har betydning for kvartseksponering på tværs af fag. Kvartseksponering er foreslået som risikofaktor for flere autoimmune reumatologiske sygdomme. Det er baseret på et begrænset antal studier, og særligt er der få studier med kvantitative mål for eksponeringen og analyser af eksponerings-responssammenhængen. Formålet med Quartz-projektet var at undersøge kvartseksponering på tværs af fag i Danmark og sammenhængen mellem kvartseksponering og autoimmune reumatologiske sygdomme.

I 2018 gennemførte vi et eksponeringsstudie blandt ansatte indenfor 11 jobgrupper med 189 personlige målinger af respirabelt støv og kvartsstøv (35 % gentagne målinger) gennem en fuld arbejdsdag. Vi undersøgte hvilke arbejdsforhold, som havde betydning for eksponeringsniveauet. De gennemsnitlige kvartseksponeringsniveauer var generelt lave (<25 µg/m3). Enkelte af de inkluderede fag havde betydeligt højere gennemsnitlige niveauer mellem 50-100 µg/m3. Blot 15 % af studiepersonerne rapporterede, at de anvendte åndedrætsværn på måledagen. Brug af elektrisk værktøj og kvartsindholdet i de anvendte materialer var de arbejdsforhold, der havde størst betydning for høje eksponeringsniveauer på tværs af fag. Disse faktorer forklarede også en stor del af forskellen i eksponeringsniveauer mellem virksomhederne, og forskellen i niveauet mellem personer med samme fag på samme virksomhed.

Vi anvendte den danske erhvervskohorte (DOC*X) til at undersøgte sammenhængen mellem kvartseksponering og systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars-vaskulitter, som alle er autoimmune reumatologiske sygdomme. Studiepopulationen bestod af alle indbyggere i Danmark, som var født efter 1955 og beskæftiget minimum 1 år mellem 1977-2015. Alle personer fik tildelt et årligt eksponeringsniveau baseret på information om jobkode fra nationale registre og en kvantitativ job eksponeringsmatrice (JEM). JEM estimaterne var modeleret ud fra historiske kvartsstøvmålinger fra europæiske og canadiske arbejdspladser samt ekspertvurderinger. Vi identificerede cases i det nationale patientregister, og undersøgte kønsspecifikke incidens rate ratioer (IRR) for de autoimmune reumatologiske sygdomme. Justeret for alder og kalenderår, og ved sammenligning af højt eksponerede med ikke eksponerede, så vi en samlet forøget risiko for de autoimmune reumatologiske sygdomme på 1.53 (1.41-1.75) blandt mænd og 1.09 (0.87-1.37) blandt kvinder. Sammenhængen var tydeligst for systemisk sklerodermi og reumatoid artritis. Resultaterne blandt kvinder var usikre, men der var få eksponerede kvinder. Der var indikation på eksponerings-respons sammenhæng og vores resultater tyder på, at eksponering, der ligger mere end 20 år tidligere, har størst betydning for den forøgede risiko.

Ved at kombinere de danske registre med en international kvantitativ job eksponerings matrice har vi fået ny og mere deltaljeret viden om sammenhængen mellem eksponering for kvarts og flere sjældne autoimmune reumatologiske sygdomme, som bidrager til forståelse af disse sygdommes epidemiologi. Projektet har bidraget med ny viden om aktuelle danske kvarts eksponeringsniveauer og hvilke forhold, der har betydning for eksponering på tværs af fag. Dette er viden, der kan anvendes direkte i det forebyggende arbejdsmiljø arbejde.

Abstract

Quartz is present in sand, stones, rocks and products made hereof, for instance concrete, bricks, tiles and other ceramic products. Workers within construction, farming, quarries, mining, and the production industri are exposed to respirable quartz (crystalline silica). We have limited knowledge on current exposure levels in Denmark and determinants of exposure levels across occupations. Quartz is suggested as a risk factor for a number of autoimmune rheumatic diseases. However, this is based on a limited number of studies, and especially few studies with quantitative exposure assessment and analysis of exposure-response relation. The aim of the Quartz-project was to examine quartz exposure concentrations across occupations in Denmark and the association between quartz exposure and autoimmune rheumatic diseases.

We conducted an exposure study with 189 personal full-shift measurements of respirable dust and quartz dust (35 % repeated measurements) among workers within 11 occupations, and we examined determinants for quartz exposure across occupations. Generally, we found that average quartz exposure concentrations were low (<25 µg/m3) in a number of occupations in Denmark, 2018. A few of the included occupations did have average exposure concentrations between 50-100 µg/m3. Only 15 % of the study population reported using a respirator. Use of power tools and quartz content in material worked on were the main determinants for quartz exposure concentration, and did also explain much of the difference in exposure between companies and between workers from same occupation and same company.

We used the Danish Occupational Cohort (DOC*X) to examine the association between quartz (silica) exposure and systemic sclerosis, reumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis. The study population consisted of all Danes born from 1956- and ever employed between 1977-2015. All persons were assigned a yearly exposure level based on job codes retrieved from national employment registers and a quantitative job exposure matrix modelled from measurements of quartz exposure at workplaces across Europe and Canada together with expert assessment. We identified cases in the national patient register and examined sex-specific incidens rate ratios (IRR) for autoimmune rheumatic diseases. Adjusted for age and calendar-year, comparing the highest exposed with non-exposed, we observed an increased risk of autoimmune rheumatic disease of autoimmune rheumatic diseases combined of 1.53 (1.41-1.75) among men and of 1.09 (0.87-1.37) among women. The association was most evident for rheumatoid arthritis and systemic sclerosis. The association was less clear among women; however few women were exposed. We found indications of exposure-response association, and furthermore our results suggest that exposure received more than 20 years earlier are most important for the association.

Combining the Danish registers with an international quantitative job exposure matrix resulted in new and more detailed knowledge on the association between quartz exposure and a number of rare autoimmune rheumatic diseases, adding to our understanding of the epidemiology of these diseases. The project adds information on current quartz exposure in Denmark and determinants across occupations, which can be used directly in preventive initiatives in the work environment.

Projektets formål

Baggrund

Kvarts er den mest almindelig form af krystallinsk siliciumdioxid ($cSiO_2$). Det findes naturligt i sand, sten, klipper og menneskabte materialer produceret herfra, som beton, mursten, tegl og keramiske produkter(1, 2). Arbejdere indenfor bygge-anlæg, landbrug, mineraludvinding og fremstillingsindustri udsættes for fint kvartsstøv, når materialerne anvendes eller bearbejdes med værktøj(2-4). På trods af generelt aftagende eksponeringsniveauer gennem de senest 50 år (3, 5-7), rapporteres der fortsat høje niveauer (8-12). Kvartseksponering er en veletableret risikofaktor for lungefibrose (13) og for lungekræft (2, 14), og er klassificeret som et gruppe-I karcinogen af WHO(2). Tilbage i 1930'erne blev kvarts eksponering forbundet med øget dødelighed pga. reumatologiske sygdomme(15), og siden er sammenhængen mellem kvarts og en række autoimmune reumatologiske sygdomme forsøgt afdækket i forskellige epidemiologiske studier: systemisk sklerodermi (16-19) og reumatoid artritis (leddegigt) (19-26), herudover er der enkelte studier omhandlende systemisk lupus erythematosus (27-29) og småkars vaskulitter (30-35).

De autoimmune reumatologiske sygdomme er karakteriseret af auto-antistoffer, som medfører at personens immunsystem angriber egne celler og proteiner medførerende inflammation og ødelæggelse af væv og organer(36, 37). Sygdommene er sjældne, med en samlet prævalens i Danmark på ca. 1 %(38). Det er kroniske sygdomme, som ikke kan kurreres og medfører høj morbiditet og mortalitet (39, 40). Sygdommene diagnosticeres oftest i den arbejdsdygtige alder, særligt blandt kvinder (41-45). Med baggrund i tvillingestudier, formodes det, at sygdommene skyldes et sammenspil mellem genetik, epigenetik og miljøfaktorer (36, 37, 46).

De fleste af studierne, der undersøger associationen mellem kvarts og sygdommene har ikke kvantitative mål for eksponeringen. Der er få egentlige analyser af eksponerings-responssammenhængen (22, 23), øvrige eksponerings-respons analyser begrænser sig til mere kvalitative mål som sammenligning af intet, høj, meget højt eksponeret (16, 18, 29, 31, 47). Kortlægning af mulig eksponerings-responssammenhæng er et centralt element i vurdering af årsagssammenhæng, og har betydning for planlægning af forebyggelsen af sygdomme blandt kvartsstøvseksponerede. Ligeledes er viden om, hvilke forhold, der har betydning for eksponering på tværs af fag, særdeles relevant i forebyggelse øjemed.

Formål

Hovedformålet med Quartz-projekt er at forebygge autoimmune sygdomme i hud, lunger, kar og led forårsaget af udsættelse for kvarts på arbejdet
Der er tre specifikke delmål:

1. at undersøge om der er årsagssammenhæng mellem udsættelse for kvartsstøv på arbejdet og systemisk sklerodermi, leddegigt, systemisk lupus erythematosus og småkars vaskulitis.
2. at beskrive eksponeringsrespons-sammenhæng mellem udsættelse for kvartsstøv på arbejdet og disse autoimmune sygdomme samt afdække eventuelle tærskelværdier.
3. at undersøge hvilke arbejdsforhold inden for en række fag og brancher som medfører udsættelse for høje niveauer af kvartsstøv i dagens Danmark

Projektets metode og udførelse

Quartz-projektet omfatter et eksponeringsstudie for at undersøge delmål 3 og et stort registerstudie for at undersøge delmål 1 og 2.

Kvarts eksponeringsstudiet

Virksomheder og studiedeltagere

Vi identificerede 14 hyppigt forekommende faggrupper ud fra DISCO 88, den danske version af ISCO-88 (International Standard Classification of Occupations, 1988) (49). De udvalgte fag havde baseret på litteraturen formodet moderat-højt kvarts eksponeringsniveauer(2, 3, 56). Vi inviterede store og små virksomheder til at deltage i arbejdspladsmålinger af kvartsstøv, og hvis muligt virksomheder med ansatte fra mere end en faggruppe og gerne lokaliseret i Østjylland. I alt kontaktede vi 38 virksomheder; 15 med ≥100 ansatte og 23 med <100 ansatte. 24 virksomheder accepterede invitationen, heraf 60% af de store virksomheder og 65 % af de små. Det lykkede ikke at inkludere landmænd.

På arbejdspladsen blev formanden instrueret i at finde op til 8 personer, der var villige til at deltage og som udførte arbejdsopgaver, som var repræsentative for faggruppen.

Støvmålinger og analyse

Alle deltager udfyldte en dagbog på måledagen over primære arbejdsopgaver, brug af værktøj/maskiner, arbejdssted (inde/ude) og brug af åndedrætsværn. Virksomhederne blev adspurgt om at deltage i 2. målerunde, og ved tilsagn, blev der udført gentagen måling på de studiepersoner, som stadig var på arbejdspladsen. Alle målinger blev udført af mellem april og oktober 2018.

Måleudstyr blev monteret forud for arbejdet, afmonteret efter endt arbejdsdag og pauseret under pauser af mere end 15 minutters varighed. I de statistiske analyser inkludere vi målinger med varighed over 4 timer. Støv blev opsamlet på et 25 mm PVC filter, monteret i en kassette (SKC LTD conductive plastic cyclone) på personens brystkasse inden for 30 cm af indåndingszonen. Kassetten blev forbundet til en pumpe, som blev kalibreret til et flow på 2,2 l/min.

Koncentrationen af respirabelt støv blev bestemt ved vejning af filteret og kvartsindhold blev bestemt med infrarød spektrometry (FTIR), i overensstemmelse med internationale standarder (HSE, MDHS 101/2) (57). Detektionsgrænsen (værdier<LOD, limit of detection) for respirabelt støv blev udregnet som 3*Standard Deviationen(SD) på vægtændring på blindfiltre, som var inkluderet ved alle målebesøg. Den analytiske detektionsgrænse for kvarts var fra laboratoriet fastsat til 10 µg.

Statistisk analyse

Koncentrationen af respirabelt støv og kvartsstøv var normal fordelt, under antagelse af at værdier under detektionsgrænsen fulgte samme fordelingskurve. Statistiske analyser blev således udført på log-transformerede værdier. Vi anvendte en mixed effects Tobit model (metobit, Stata), hvor alle værdi under LOD antages at være indenfor et interval mellem (-∞) og LOD (58, 59). Person, virksomhed og fag blev inkluderet som "random effects" og værktøj, arbejdssted og fraktionen af kvarts i respirabelt støv som "fixed effects".

I analyserne blev DISCO-88 fag anvendt på 4 ciffer niveau, men ved mindre end 10 personer i gruppen, blev faget slået sammen med nærmeste gruppe på 3 ciffer niveau. Industri blev opgjort på 2 ciffer niveau baseret på 2.version af den Europæiske industriklassifikation, NACE(60). Værktøj blev kategoriseret som intet, brug af manuelt værktøj, brug af elektrisk værktøj eller brug af større maskiner og køretøjer. Arbejdssted blev kategoriseret til primært inde eller ude. Til beregning af fraktionen af kvarts i respirabelt støv, var det nødvendigt at lave en modellering af værdier under LOD, som primært blev baseret på øvrige målinger inden for samme job og virksomhed.

Registerstudiet

Studiepopulation

Studiepopulationen bestod af alle danskere med minimum ét års lønnet arbejde mellem 1977-2015 registreret i den danske erhvervskohorte DOC*X (the Danish Occupational Cohort, DOC*X) (48). DOC*X indeholder årlig information om alle danske statsborgeres beskæftigelse og job kodet ud fra DISCO-88 (49). For at opnå fuld erhvervshistorik inkluderede vi danskere født fra 1956 og frem, og fra CPR registret fik vi oplysninger til at ekskludere døde, emigrerede eller forsvundne før opfølgningsperiodens start i 1979 (50).

I Landspatient Registeret identificerede vi alle tilfælde af systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars vaskulitter diagnosticeret fra danske sygehus afdelinger (1977-) og speciallægeklinikker (1995-) (51).

Ud fra årlig jobkode fik alle personer i studiepopulationen tildelt et årligt estimat for kvarts eksponering baseret en international jobeksponeringsmatrice, SYNJEM (3, 52). SYNJEM er modelleret ud fra ekspertvurderinger samt 23.640 personbårne kvartsstøvmålinger på arbejdspladser i Danmark, samt andre europæiske lande og Canada. SYNJEM indeholder års- og regionsspecifikke kvantitative estimater for kvarts (respirabelt silica) eksponering for alle jobkoder i ISCO-68. I Quartz-projektet anvendte vi estimater for de nordiske lande samt en konverteret udgave med ISCO-88 estimater. For alle personer beregnede vi den kumulerede eksponering, dvs. summen af eksponering i alle eksponerede år (µg/m^3-år). Vi anvendte også gennemsnitlig eksponeringsniveau (kumuleret eksponering delt med varighed (µg/m^3)), højest opnåede eksponeringsniveau (µg/m^3) og eksponeringsvarighed(år).

Fra registrene er information om beskæftigelse opgjort på årsbasis, hvorfor alle uafhængige variable blev forskudt med et år.

Alle studiepersoner blev fulgt fra året efter første beskæftigede år, dog tidligst fra 1979, to år efter Landspatientregisteret blev etableret, for ikke at inkludere prævalente cases. Årlig opfølgning fortsatte indtil første år med diagnose af systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus, småkars vaskulitis, død, emigration eller ophør af studieperioden (31.12.2015).

Statistiske analyser

Med person-år som analyseenhed i logistiske regressions analyser undersøgte vi sammenhængen mellem kvarts eksponering og de fire autoimmune reumatologiske sygdomme både hver for sig og samlet (53). I disse analyser blev studiepopulationen delt i fire grupper: en ikke-eksponeret og en lav, mellem og højt eksponeret, hvor de eksponerede blev opdelt i tre lige store grupper beregnet ud fra eksponerede person-år. Vi undersøgte associationen ved eksponering indenfor forskellige tidsvinduer (de foregående 1-10, 11-20 og >20 år), og til dette blev eksponering uden for det specifikke vindue klassificeret som 0, og al eksponering i det angivne tidsrum blev delt i to baseret på medianen af eksponerede person-år (54). Vi undersøgte den log-lineære sammenhæng med kvarts som kontinuerlig variable i den fulde population og i interne analyser begrænset til eksponerede person-år. Vi lavede kubiske spline-modeller, hvor knudepunkterne blev placeret 40, 60 og 80 percentilen af den kumulerede eksponering.

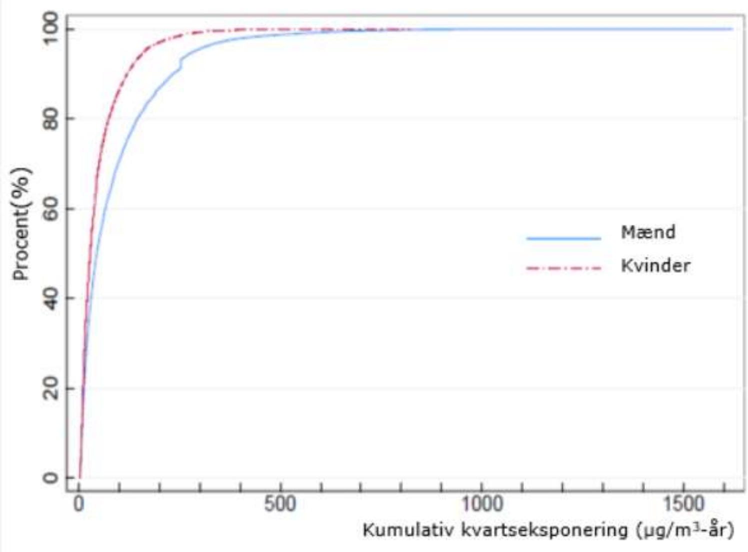
Alle hovedanalyser blev stratificeret på køn, og justeret for alder og kalenderår. For at tage hensyn til mulig confounding fra socio-økonomiske faktorer foretog vi sensitivitets analyser, hvor vi inkludere sandsynligheden for rygning med en tobaks-JEM (55), højst opnået uddannelsesniveau samt analyser begrænset til en studiepopulation bestående af håndværkere, industri-, landbrugs- eller ufaglærte arbejdere (ISCO hovedgruppe 6-9) ved baseline.

Resultater: om projektets formål er opnået

Kvartseksponering i erhvervskohorten og blandt 11 danske faggruppe

Erhvervskohorten af alle indbyggere i Danmark født efter 1955 med minimum ét års lønnet arbejde 1977-2015 bestod af 1.541.505 mænd og 1.470.769 kvinder. Baseret på registre og den kvantitative jobeksponeringsmatrice har 309.239 personer en ansættelse med sandsynlig kvartseksponering, det svarer til hhv 17% og 3 % af alle de erhvervsaktive mænd og kvinder i perioden. Som det fremgår af figur 1, er mændenes gennemsnitlige (medianen) kumulative eksponeringsniveau på 60 µg/m^3-år (25 til 75 percentilen: 23-135 µg/m^3-år) højere end kvindernes på of 33 µg/m^3-år (16-72 µg/m^3-år).

Figur 1. Kumulativ plot af distribueringen af kumulativ kvarts eksponeringsniveau (µg/m^3-år) ved opfølgningsperiodens afslutning blandt 266.325 mænd og 42.914 kvinder, der har minimum et års ansættelse med kvartseksponering.



I studiepopulationen bestående af personer fra 11 hyppigt forekommende faggrupper fandt vi, at de gennemsnitlige kvartseksponeringsniveauer inden for en række af disse fag er lave, men enkelte fag har gennemsnitlige niveauer tæt ved arbejdstilsynets (ATs) grænseværdi for respirabelt kvarts (100 µg/m^3) (Tabel 1). Flere af fagene har gennemsnitlige niveauer omkring eller over 25 µg/m^3, som er den tærskelværdi (Threshold limit value, TLV) som American Conference of Governmental Industrial Hygienists (ACGIH) anbefaler. Baseret på geometrisk mean (GM) og spredningen (GSD) i vores sample er der en sandsynlighed på 48 % for at aktuelle grænseværdi på 100 µg/m^3 overskrides blandt stenhuggere, og en sandsynlighed mellem 14-18 % for at grænseværdien overskrides blandt bygningsarbejderne (murere, brolæggere, andre bygningsarbejdere), arbejdere i mineral- og stenbrud og stålværksarbejdere.

Brug af elektrisk værktøj og arbejde med materialer med højt kvartsindhold (procentvis) havde størst betydning for kvartseksponering og forklarede en del af forskellen i eksponeringsniveauer mellem virksomhederne og mellem arbejdere indenfor samme fag og virksomhed. 15 % af personerne rapporterede, at de havde anvendt åndedrætsværn i løbet af arbejdsdagen.

Tabel 1. Karakteristik af respirabelt støv og kvarts støv (µg/m³) blandt 140 personer, Danmark, 2018

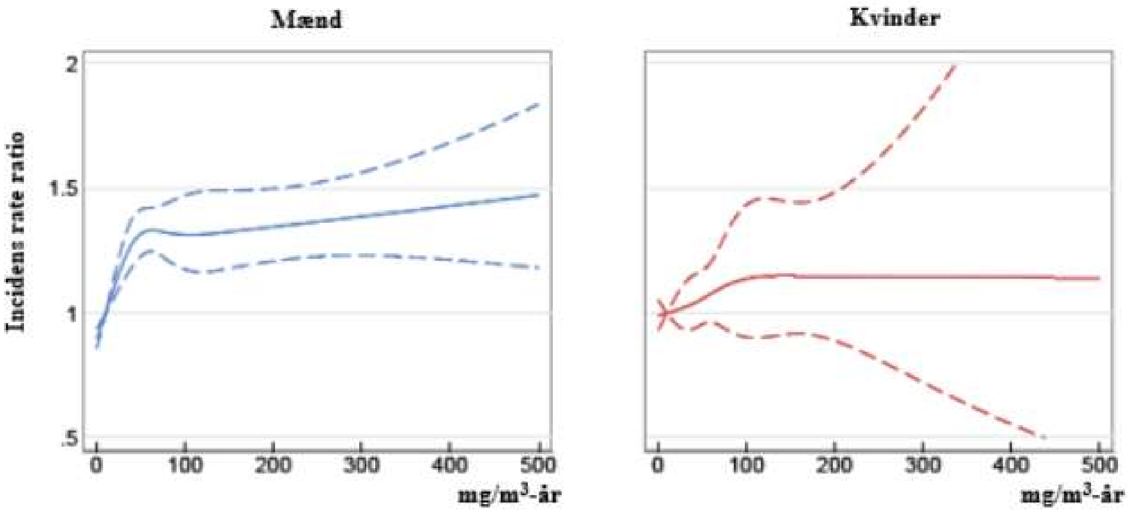
	Personer	Prøver	Respirabelt støv		Kvartsstøv		Respirabelt støv µg/m³			Kvartsstøv µg/m³			% kvarts i respirabelt støv	Kvarts µg/m³ (>LOD) min-max	Exceedance (%)[f]
Karakteristik	K	N	<LOD[a]	%	<LOD[b]	%	AM[c]	GM[d]	GSD[e]	AM[c]	GM[d]	GSD[e]			
Faggruppe (DISCO-88)															
7113. Stenhuggerarbejde	10	15	0	0	0	0	1224	534	3.44	199	93	3.47	18	20-1083	48
7122. Murer- og brolægningsarbejde	17	24	3	13	9	38	260	86	5.32	57	21	4.36	30	10-194	15
7123. Beton-, cement- og terazzoarbejde	16	23	1	4	12	52	152	114	2.30	14	8	1.92	14	9-56	< 1
7129. Bygningsarbejde (basis) i øvrigt	21	21	0	0	3	14	1554	741	2.83	57	34	2.95	7	9-179	16
7220. Grovsmede-, værktøjsmagerarbejde og lignende	9	11	0	0	7	64	1038	718	2.50	21	9	4.78	9	25-121	6
8112. Mineral- og stenbrudsanlægsarbejde	8	11	0	0	3	27	304	185	3.00	39	22	4.06	17	11-196	14
8122. Stålværksarbejde	10	18	0	0	0	0	1032	719	1.97	69	61	1.71	11	24-165	18
8131. Operatørarbejde ved glas og keramik ovne	17	22	0	0	10	45	394	297	2.27	21	12	2.26	6	10-58	1
8212. Betjening af maskiner indenfor mineral industrien	7	11	0	0	8	73	196	176	1.55	13	5	1.72	7	9-22	< 1
8332. Entreprenør-maskinførerarbejde	10	14	5	36	10	71	41	25	2.57	10	4	2.95	19	10-14	< 1
9310. Manuelt arbejde indenfor bygge- og anlægssektoren	15	19	1	5	9	47	154	94	2.88	18	10	2.49	17	10-71	1
Industri (NACE, rev.2)															
8. Råstofudvinding (sten, sand, ler)	10	14	0	0	3	21	337	209	2.90	41	22	3.41	16	11-196	11
23. Fremstilling af ikke-metalholdige mineralske produkter	34	48	0	0	18	38	597	311	2.69	72	20	4.81	10	9-1083	15
24. Fremstilling af metal	10	18	0	0	0	0	1032	746	1.97	69	60	1.71	11	24-165	17
25. Jern og metalvare industri (excl. maskiner)	7	8	0	0	7	88	1200	888	2.45	13	3	3.75	8	25-25	< 1
41. Opførelse af bygninger	7	14	1	7	11	79	136	88	2.73	16	5	3.85	25	11-55	1
42. Anlægsarbejde	16	21	0	0	12	57	169	111	2.48	19	8	3.11	16	10-71	1
43. Bygge og anlægsvirksomhed, der kræver specialisering	56	66	9	14	20	30	688	153	6.68	42	18	3.58	16	9-194	9
Værktøj															
Intet	15	19	0	0	11	58	424	254	2.47	19	8	2.40	8	9-58	< 1
Brug af manuelt værktøj	44	72	4	6	32	44	398	197	3.98	33	15	3.82	17	10-165	8
Brug af elektrisk værktøj	40	46	0	0	8	17	1224	462	4.15	90	30	4.36	13	9-1083	21
Brug af større maskiner og køretøjer	41	52	6	12	20	38	287	110	4.37	26	13	3.27	16	9-196	4
Arbejdsplads															
Indendørs	68	93	0	0	27	29	916	478	2.78	62	23	3.82	10	9-776	14
Udendørs	72	96	10	10	44	46	309	100	4.33	30	12	4.11	19	9-1083	6
Total	140	189	10	5	71	38	604	216	4.42	46	16	4.07	15	9-1083	10

[a] Limit of Detection (LOD), detektionsgrænsen for respirabelt støv = 24 µg/m³, [b] Limit of Detection (LOD)), detektionsgrænsen for respirabelt kvarts =9 µg/m³, [c] AM: Arimetrisk Mean, [d] GM: Geometrisk Mean, [e]GSD: Geometrisk Standard Deviation, [f] Exceedance (forventet overskridelse) af OEL 100 µg/m³

Kvartseksponering og autoimmune reumatologiske sygdomme

Fra landspatient registret identificerede vi 4673 mænd og 12.268 kvinder diagnosticeret med en eller flere af de autoimmune reumatologiske sygdomme, fordelt på sygdommene (oplistet mænd/kvinder) systemisk sklerodermi (n=252/746), reumatoid artritis (n=3490/9190), systemisk lupus erythematosus (n=255/1821) og småkars vaskulitter (n=749/869).

Blandt mænd, så vi en øget incidens rate ratio på 1,53 (95 % sikkerhedsinterval: 1,39-1,69) for autoimmune reumatologiske sygdomme, når vi sammenlignede mænd med den højeste kumulerede eksponering med ikke eksponerede mænd og justerede for alder og kalenderår. I analyser af hele populationen fandt vi en trend på 1,07 (1,05-1,09) pr. 50 µg/m^3-år, og i analyser begrænset til de eksponerede var trenden på 1,03 (1,00-1,05) pr. 50 µg/m^3-år (Tabel 2, figur 2). Sammenhængen mest tydelig for systemisk sklerodermi og reumatoid artritis. Resultaterne var mere inkonsistent for systemisk lupus erythematosus og småkars vaskulitter. Vi fandt indikation på eksponerings-respons sammenhæng blandt mændene, men kunne ikke fastsætte tærskelværdi.



Figur 2. Kubiske splines af de alder og kalenderårsjusterede incidens rate ratioer for autoimmune reumatisk sygdomme efter kumuleret kvartseksponering blandt 1.541.505 mænd og 1.470.769 kvinder, 1979-2015

I analyser med andre eksponeringsmål (gennemsnitlig eksponeringsniveau, højest opnåede eksponeringsniveau og eksponeringsvarighed) så vi et tilsvarende mønster, hvor risikoen øges med højere eksponeringsniveauer. I analyser af eksponering i forskellig tidsvinduer, så vi en tendens til at eksponering, der ligger mere en 20 år tidligere har større betydning for sygdomsrisiko end nylig eksponering (Tabel 3).

I analyser af kvindernes risiko, så vi mønstre, der lignede mændenes, men resultaterne er mere usikre. Når vi sammenlignede de højest kumulativt eksponerede kvinder med de ikke eksponerede og justerede for alder og kalenderår, så vi en øget incidens rate ratio på 1,09 (0,87-1,37) for autoimmune reumatologiske sygdomme. I analyser af hele populationen og begrænset til de eksponerede fandt vi trends på hhv. 1,04 (0,99-1,10) og 1,03 (0,96-1,12) pr.

50 µg/m3-år (Tabel 1). Interaktionsanalyser af køn i vores studiepopulationen gav ikke grundlag for at tro, at risikoen ved kvartseksponering er forskellig for mænd og kvinder.

I analyser, hvor vi tog hensyn til potentiel confounding fra faktorer relateret til socioøkonomisk status (sandsynligheden for tobaksrygning, uddannelsesniveau eller begrænsede populationen til håndværkere, industriarbejdere, landbrugs- eller ufaglærte arbejdere), så vi fortsat en forøget risiko med incidens rate ratio på hhv. 1,44 (1,31-1,59), 1,37 (1,24-1,51) og 1,44 (1,30-1,59) for autoimmune reumatologisk sygdomme, når man sammenlignede de højest eksponerede mænd med ikke-eksponerede mænd.

Tabel 2. Incidens rate ratioer (IRR) med 95 % sikkerhedsinterval for alle autoimmune reumatologiske sygdomme samt for systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars vaskulitter hver for sig, opdelt efter kvarts eksponering blandt 1.541.505 mænd og 1.470.769 kvinder, Danmark, 1979-2015

	Mænd												
	Autoimmune reumatologiske sygdomme [a]			Systemisk sklerodermi		Reumatoid artritis		Systemisk lupus erythematosus		Småkars vaskulitter	
Eksponering	Person-år [b]	cases	IRR[c] (95 % CI)	Cases	IRR[c] (95 % CI)	Cases	IRR[c] (95 % CI)	Cases	IRR[c] (95 % CI)	Cases	IRR[c] (95 % CI)
Kumulativ kvarts eksponering (µg/m^3-år)											
0	28.527.938	3.563	1	203	1	2.630	1	198	1	587	1
2,0-29,2	1.576.698	283	1,23 (1,09-1,39)	8	0,69 (0,34-1,40)	218	1,24 (1,08-1,43)	18	1,42 (0,88-2,31)	46	1,34 (0,99-1,80)
29,3-93,9	1.639.692	351	1,42 (1,27-1,58)	14	1,04 (0,60-1,79)	267	1,42 (1,25-1,61)	16	1,22 (0,73-2,04)	57	1,54 (1,17-2,02)
94,0-1622	1.784.974	476	1,53 (1,39-1,69)	27	1,62 (1,08-2,44)	375	1,57 (1,41-1,75)	23	1,46 (0,94-2,27)	59	1,34 (1,02-1,76)
Pr 50 µg/m^3-år			*1,07 (1,05-1,09)*		*1,10 (1,03-1,18)*		*1,07 (1,05-1,10)*		*1,09 (1,01-1,17)*		*1,06 (1,01-1,11)*
Pr 50 µg/m^3-år (blandt eksponerede)			*1,03 (1,00-1,05)*		*1,11 (1,02-1,21)*		*1,02 (0,99-1,05)*		*1,06 (0,96-1,18)*		*0,99 (0,93-1,07)*
	Kvinder										
	Autoimmune reumatologiske sygdomme [a]			Systemisk sklerodermi		Reumatoid artritis		Systemisk lupus erythematosus		Småkars vaskulitter	
	Person-år [b]	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)
Kumulativ kvarts eksponering (µg/m^3-år)											
0	30.800.795	11.888	1	716	1	8.906	1	1.767	1	846	1
2,0-29,2	340.301	156	0,99 (0,84-1,16)	12	1,36 (0,77- 2,40)	114	0,93 (0,78- 1,12)	25	1,18 (0,79-1,75)	9	0,87 (0,45-1,69)
29,3-93,9	278.490	148	1,12 (0,95-1,31)	12	1,56 (0,88-2,76)	110	1,07 (0,88-1,29)	22	1,26 (0,83-1,93)	8	0,94 (0,47-1,88)
94,0-1622	133.920	76	1,09 (0,87-1,37)	6	1,46 (0,65-3,27)	60	1,10 (0,85-1,42)	7	0,82 (0,39-1,73)	6	1,38 (0,62-3,08)
Pr 50 µg/m^3-år			*1,04 (0,99-1,10)*		*1,14 (0,95-1,36)*		*1,05 (0,98-1,11)*		*1,04 (0,89-1,22)*		*1,03 (0,82-1,29)*
Pr 50 µg/m^3-år (blandt eksponerede)			*1,03 (0,96-1,12)*		*1,04 (0,78-1,38)*		*1,05 (0,97-1,15)*		*0,98 (0,78-1,24)*		*1,10 (0,82-1,47)*

[a] Autoimmune reumatologiske sygdomme: Systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars vaskulitter. [b] Antal person-år for de sygdomsspecifikke analyser varierede en smule, i tabellen er kun vist person-år for alle sygdomme, mens de specifikke antal er anvendt i analyserne. [c] Justeret for alder (≤25, 26-35, ≥36) og kalenderår (1979-1985, 1986-1995, 1996-2005, 2006-2015).

Tabel 3. Incidens rate ratios (IRR) med 95 % sikkerhedsinterval for autoimmune reumatologiske sygdomme, samt for systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars vaskulitter hver for sig, efter kvarts eksponering i de foregående 1-10, 11-20 og >20 år tidsvinduer blandt 1.541.505 mænd og 1.470.769 kvinder, Danmark, 1979-2015

Mænd	Autoimmune reumatologiske sygdomme [a]			Systemisk sklerodermi		Reumatoid artritis		Systemisk lupus erythematosus		Småkars vaskulitter	
Kumulativ kvarts eksponering ($\mu g/m^3$-år)	Person-år [b]	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)
1-10 år											
0	29.829.503	3.975	1	217	1	2.953	1	217	1	650	1
2,0-37,1	1.779.056	355	1,36 (1,22-1,51)	19	1,45 (0,90-2,31)	271	1,36 (1,20-1,54)	18	1,26 (0,78-2,04)	55	1,38 (1,05-1,82)
37,2-875,2	1.920.743	343	1,30 (1,16-1,45)	16	1,02 (0,61-1,70)	266	1,36 (1,20-1,55)	20	1,37 (0,86-2,17)	44	1,03 (0,76-1,41)
Pr 50 $\mu g/m^3$-år			*1,10 (1,04-1,16)*		*1,07 (0,87-1,31)*		*1,12 (1,06-1,19)*		*1,14(0,93-1,39)*		*1,00 (0,87-1,16)*
11-20 år											
0	31.276.025	4.038	1	222	1	2.986	1	223	1	668	1
3,5-47,6	1.081.784	302	1,42 (1,27-1,60)	16	1,64 (0,98-2,75)	227	1,36 (1,19-1,56)	15	1,40 (0,82-2,37)	51	1,80 (1,35-2,41)
47,7-875,2	1.171.493	333	1,46 (1,30-1,63)	14	1,27 (0,73-2,20)	277	1,54 (1,36-1,75)	17	1,54 (0,93-2,55)	30	1,00 (0,69-1,45)
Pr 50 $\mu g/m^3$-år			*1,13 (1,08-1,18)*		*1,16 (0,97-1,38)*		*1,14 (1,09-1,20)*		*1,14 (0,94-1,37)*		*1,01 (0,88-1,16)*
>20 år											
0	32.434.659	4.242	1	230	1	3.153	1	236	1	689	1
6,1-66,6	521.145	184	1,42 (1,23-1,66)	7	1,28 (0,59-2,75)	145	1,40 (1,18-1,66)	10	1,72 (0,90-3,29)	25	1,52 (1,01-2,29)
66,7-1338,5	573.498	247	1,70 (1,49-1,94)	15	2,48(1,44-4,27)	192	1,65 (1,42-1,92)	9	1,37 (0,69-2,71)	35	1,87 (1,32-2,66)
Pr 50 $\mu g/m^3$-år			*1,13 (1,10-1,17)*		*1,22 (1,09-1,36)*		*1,12 (1,08-1,16)*		*1,15 (1,00-1,32)*		*1,17 (1,08-1,26)*
Kvinder											
Kumulativ kvarts eksponering ($\mu g/m^3$-år)	Person-år [b]	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)	cases	IRR[c] (95 % CI)
1-10 år											
0	31.051.236	12.066	1	731	1	9.045	1	1.790	1	854	1
2,0-37,1	319.807	134	0,98 (0,82-1,16)	10	1,26 (0,68-2,36)	93	0,89 (0,72-1,09)	24	1,23 (0,82-1,83)	10	1,08 (0,58-2,02)
37,2-875,2	182.463	68	0,97 (0,76-1,23)	5	1,08 (0,45-2,61)	52	1,00 (0,76-1,31)	7	0,65 (0,31-1,36)	5	1,00 (0,41-2,40)
Pr 50 $\mu g/m^3$-år			*1,00 (0,87-1,15)*		*0,92 (0,52-1,63)*		*1,00 (0,85-1,19*		*0,96 (0,67-1,38)*		*0,99 (0,60-1,65)*
11-20 år											
0	31.252.372	12.085	1	732	1	9.050	1	1.798	1	n.r	1
3,5-47,6	194.665	118	1,09 (0,91-1,31)	9	1,54 (0,79-2,97)	88	1,02 (0,83-1,26)	15	1,14 (0,69-1,90)	n.r	1,40 (0,73-2,71)
47,7-875,2	106.469	65	1,08 (0,84-1,38)	5	1,51 (0,62-3,64)	52	1,08 (0,82-1,42)	8	1,14 (0,57-2,29)	n.r	0,58 (0,14-2,31)
Pr 50 $\mu g/m^3$-år			*1,03 (0,92-1,16)*		*1,16 (0,75-1,77)*		*1,02 (0,89-1,17)*		*1,06 (0,76-1,48)*		*0,96 (0,56-1,65)*
>20 år											
0	31.417.074	12.150	1	736	1	9.096	1	n.r	1	n.r	1
6,1-66,6	92.154	79	1,27 (1,01-1,58)	5	1,48 (0,61-3,57)	62	1,22 (0,95-1,57)	n.r	1,91 (1,08-3,38)	n.r	1,09 (0,41-2,93)
66,7-1338,5	44.278	39	1,30 (0,95-1,78)	5	3,06 (1,27-7,40)	32	1,31 (0,92-1,85)	n.r	0,66 (0,17-2,65)	n.r	1,69 (0,54-5,27)
Pr 50 $\mu g/m^3$-år			*1,12 (1,02-1,24)*		*1,36 (1,06-1,74)*		*1,14 (1,02-1,26)*		*1,15 (0,86-1,53)*		*1,13 (0,77-1,66)*

[a] Autoimmune reumatologiske sygdomme: Systemisk sklerodermi, reumatoid artritis, systemisk lupus erythematosus og småkars vaskulitter. [b] Antal person-år for de sygdomsspecifikke analyser varierede en smule, i tabellen er kun vist person-år for alle sygdomme, mens de specifikke antal er anvendt i analyserne. [c] Justeret for alder (≤25, 26-35, ≥36) og kalenderår (1979-1985, 1986-1995, 1996-2005, 2006-2015). n.r.: en eller flere af celler baseres på under 5 personer, hvorfor oplysning om antal cases udelades.

Konklusioner

En række epidemiologiske studier har fundet en sammenhæng mellem kvartseksponering og forskellige autoimmune reumatologiske sygdomme, men flere af studierne beror på selvrapporterede oplysning og få har kvantitative målinger. Med dette projekt tilstræbte vi at supplere den eksisterende viden ved at undersøge sammenhængen mellem objektive mål for kvartseksponering og udvalgte autoimmune sygdomme; reumatoid artritis, systemisk sklerodermi, systemisk lupus erythematosus og småkars-vaskulitter. For at komme nærmere en forståelse af kausalitet ville vi undersøge eksponerings-respons, og hvis muligt tærskelværdier. Da kvartseksponering er uundgåelig i en række fag, har vi brug for opdateret viden om eksponeringsniveauer blandt danske arbejdstagere og ikke mindste, hvilke forhold der bidrager hertil for at kunne planlægge en effektiv forebyggelsesstrategi.

Vores studier understøtter en sammenhæng mellem kvartseksponering og autoimmune reumatologiske sygdom. Dette var tydeligst blandt mænd, og ved reumatoid artritis og systemisk sklerodermi, men vi fandt en tendens mod at det samme gjaldt for kvinder og for sygdommene systemisk lupus erythematosus og småkars-vaskulitter. Resultaterne blandt kvinder var påvirket af, at der var få eksponerede kvinder. Risikoen for udvikling af autoimmune reumatologiske sygdomme steg med stigende kvarts eksponering, både når forskellig eksponeringsgrupper sammenlignedes, men også baseret på trenden modelleret af de kontinuerte data. Dette studie indikerer således en eksponerings-respons sammenhæng mellem kvarteksponering og systemisk sklerodermi samt reumatoid artritis, og muligvis også for systemisk lupus erythematosus og småkars vaskulitter. Vi kunne ikke påvise en tærskelværdi. Risikoen steg fra ikke-eksponerede til gruppen af lavest eksponerede, men dette kunne også skyldes andre forskelle i risikofaktorer, som vi ikke har kendskab til endnu.

Overordnet set er gennemsnitlige kvartseksponeringsniveauerne lave (<25 µg/m^3) inden for en række fag i Danmark, 2018. Enkelte fag havde betydeligt højere gennemsnitlige niveauer, og forebyggende tiltag for at beskytte disse arbejdstagere mod øget sygdomsrisiko er nødvendig. Personlige åndedrætsværn blev anvendt i meget begrænset omfang. Elektrisk værktøj og kvartsindholdet i de anvendte materialer var forhold med størst betydning for eksponering. Ligeledes forklarede disse faktorer en del af forskellen mellem virksomhederne og også mellem arbejdere inden for samme fag og samme virksomhed.

Perspektivering (hvordan resultater på kort og længere sigt kan bidrage til at forbedre arbejdsmiljøet)

Forbedring af arbejdsmiljøet kræver viden om omfanget af en given eksponering og risikoen for forringet helbred forbundet hermed.

Baseret på de danske registre kombineret med viden fra historiske kvartsmåling på arbejdspladser i Europa og Canada har ca. 10 % af den beskæftigede danske arbejdsstyrke på et tidspunkt i deres arbejdsliv haft et job med sandsynlig kvartseksponering. Der er således tale om en relativ hyppig eksponering. Flere studier har vist tendenser mod en aftagende trend i den generelle eksponeringsniveau for kvarts(3, 5-7). I Danmark foretages ikke systematiske målinger af kvarts i arbejdsmiljøet, og vores viden om aktuelle niveauer er baseret på historisk viden og publiceret litteratur fra andre lande. Vores studie har bidraget med viden om kvartseksponeringsniveauerne over en hel arbejdsdag fra 11 forskellige fag.

På kort sigt betyder dette at arbejdstagere, arbejdsgivere, fagorganisationens og lovgivere har mulighed for på et oplyst grundlag at træffe valg og foranstaltninger for at reducere eksponering, hvor dette er nødvendig. Anvendelse af personlig åndedrætsværn anvendes i meget begrænset omfang. Vores studie var ikke designet til at give ikke indblik i baggrundene herfor, det kræver en anden type undersøgelse. Vores studie viser at brug af elektrisk værktøj og kvartsindholdet i materialerne havde størst betydning for eksponeringsniveauer, og fokus på dette i forebyggelsesøjemed vil have betydning for effektiv nedsættelse af kvartseksponeringsniveauer.

Ud over de veldokumenterede effekter af kvartseksponering i form af lungefibrose (silikose) og lungekræft, understøtter vores studie den eksisterende litteratur, der peger mod en sammenhæng mellem kvartsstøveksponering og autoimmune reumatologiske sygdomme. Vores studie bidrager med viden om en sandsynlig eksponerings-respons association, der taler for kausalitet i årsagssammenhængen. Dette bringer os også i lille skridt videre i forståelsen af samspillet mellem det omgivende miljø og de autoimmune sygdomme. De autoimmune sygdomme er præget af tilstedeværelsen af en eller flere forskellige typer af autoantistoffer, dvs antistoffer rettet mod kroppens egne proteiner, celler mm. Undervejs i projektet, erkendte vi, at for at komme nærmere en forståelse af mekanismen mellem kvartseksponering og sygdommene, har vi behov for specifikt at undersøge denne sammenhæng. Vi har fået adgang til blodprøvesvar på forskellige autoantistoffer fra Statens Serum Institut og er i gang med at analysere disse. Vi har endnu ikke færdige peer-reviewed resultater, der kan indgå i denne rapport.

Quartz-projektet er et eksempel på at et internationalt samarbejde, og kombinationen af en jobeksponeringsmatrice baseret på kvantitative målinger med de omfattende danske registerdata, kan tilvejebringe ny viden om risikofaktorer for sjældne, men alvorlige sygdomme. Kombineret med et eksponeringsstudie med undersøgelse af hvilke forhold, der har betydning for eksponering, giver det mulighed for at agere på vores nye viden om risikofaktorer.

Projektet er støttet af Arbejdsmiljøforskningsfonden (bevilling nr. 34-2016-09).

Referenceliste

1. IOM. SHEcan report: Health, socio-economic and enviromental aspects of possible amendments to the EU Directives on the protection of workers from the risks related to the exposure to carcinogens and mutagens at work Respirable chrystalline silica. Institute of Occupational Medicine (IOM); 2011.

2. IARC. Arsenic, metals, fibres, and dusts. Lyon, France: IARC working group on the evaluation of carcinogenic risks to humans, WHO; 2012.

3. Peters S, Vermeulen R, Portengen L, Olsson A, Kendzia B, Vincent R, et al. Modelling of occupational respirable crystalline silica exposure for quantitative exposure assessment in community-based case-control studies. J Environ Monit. 2011;13(11):3262-8.

4. Roney N, Faroon O, Williams M, Jones DG, Klotzbach JM, Kawa M, et al. Toxicological profile for silica. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service: Agency for Toxic Substances and Disease Registry (ATSDR); 2019.

5. Creely KS, Cowie H, Van Tongeren M, Kromhout H, Tickner J, Cherrie JW. Trends in inhalation exposure--a review of the data in the published scientific literature. Ann Occup Hyg. 2007;51(8):665-78.

6. Yassin A, Yebesi F, Tingle R. Occupational exposure to crystalline silica dust in the United States, 1988-2003. Environ Health Perspect. 2005;113(3):255-60.

7. Zilaout HA-O, Houba R, Kromhout H. Temporal trends in respirable dust and respirable quartz concentrations within the European industrial minerals sector over a 15-year period (2002-2016). Occup Environ Med. 2020;77(1470-7926 (Electronic)):268-75.

8. Radnoff D, Todor MS, Beach J. Occupational Exposure to Crystalline Silica at Alberta Work Sites. J Occup Environ Hyg. 2014;11(9):557-70.

9. Andersson L, Bryngelsson IL, Ohlson CG, Naystrom P, Lilja BG, Westberg H. Quartz and dust exposure in Swedish iron foundries. J Occup Environ Hyg. 2009;6(1):9-18.

10. Bello A, Mugford C, Murray A, Shepherd S, Woskie SR. Characterization of Occupational Exposures to Respirable Silica and Dust in Demolition, Crushing, and Chipping Activities. Ann Work Expo Health. 2019;63(1):34-44.

11. Healy CB, Coggins MA, Van Tongeren M, MacCalman L, McGowan P. Determinants of Respirable Crystalline Silica Exposure Among Stoneworkers Involved in Stone Restoration Work. Annals of Occupational Hygiene. 2014;58(1):6-18.

12. Baldwin PEJ, Yates T, Beattie H, Keen C, Warren N. Exposure to Respirable Crystalline Silica in the GB Brick Manufacturing and Stone Working Industries. Ann Work Expo Health. 2019;63(2):184-96.

13. t Mannetje A, Steenland K, Attfield M, Boffetta P, Checkoway H, DeKlerk N, et al. Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. Occupational and environmental medicine. 2002;59(11):723-8.

14. Ge C, Peters S, Olsson A, Portengen L, Schuz J, Almansa J, et al. Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks. A Pooled Analysis of Case-Control Studies. Am J Respir Crit Care Med. 2020;202(3):412-21.

15. Collis EL, Yule GU. The Mortality Experience of an Occupational Group Exposed to Silica Dust, Compared with that of the General Population and an Occupational Group Exposed to Dust not Containing Silica. Journal of Industrial Hygiene. 1933;15:395-417.

16. Diot E, Lesire V, Guilmot JL, Metzger MD, Pilore R, Rogier S, et al. Systemic sclerosis and occupational risk factors: a case-control study. Occup Environ Med. 2002;59(8):545-9.

17. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Male systemic sclerosis and occupational silica exposure-a population-based study. Aust N Z J Med. 2000;30(2):215-20.

18. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, et al. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. Autoimmunity Reviews. 2014;13(2):151-6.

19. Blanc PD, Jarvholm B, Toren K. Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers. Am J Med. 2015;128(10):1094-101.

20. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940-81. Br Med J (Clin Res Ed). 1987;294(6578):997-1000.

21. Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis. 2010;69(6):1072-6.

22. Turner S, Cherry N. Rheumatoid arthritis in workers exposed to silica in the pottery industry. Occup Environ Med. 2000;57(7):443-7.

23. Vihlborg P, Bryngelsson IL, Andersson L, Graff P. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. BMJ Open. 2017;7(7):e016839.

24. Yahya A, Bengtsson C, Larsson P, Too CL, Mustafa AN, Abdullah NA, et al. Silica exposure is associated with an increased risk of developing ACPA-positive rheumatoid arthritis in an Asian population: evidence from the Malaysian MyEIRA case-control study. Modern rheumatology / the Japan Rheumatism Association. 2013.

25. Ilar A, Alfredsson L, Wiebert P, Klareskog L, Bengtsson C. Occupation and Risk of Developing Rheumatoid Arthritis: Results From a Population-Based Case-Control Study. Arthritis Care Res (Hoboken). 2018;70(4):499-509.

26. Wrangel O, Graff P, Bryngelsson IL, Fornander L, Wiebert P, Vihlborg P. Silica Dust Exposure Increases Risk for Rheumatoid Arthritis: A Swedish National Registry Case-Control Study. J Occup Environ Med. 2021;63(11):951-5.

27. Cooper GS, Wither J, Bernatsky S, Claudio JO, Clarke A, Rioux JD, et al. Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. Rheumatology (Oxford). 2010;49(11):2172-80.

28. Finckh A, Cooper GS, Chibnik LB, Costenbader KH, Watts J, Pankey H, et al. Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. Arthritis Rheum. 2006;54(11):3648-54.

29. Parks CG, Cooper GS, Nylander-French LA, Sanderson WT, Dement JM, Cohen PL, et al. Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. Arthritis Rheum. 2002;46(7):1840-50.

30. Gregorini G, Ferioli A, Donato F, Tira P, Morassi L, Tardanico R, et al. Association between Silica Exposure and Necrotizing Crescentic Glomerulonephritis with P-Anca and Anti-Mpo Antibodies - a Hospital-Based Case-Control Study. Anca-Associated Vasculitides. 1993;336:435-40.

31. Hogan SL, Cooper GS, Savitz DA, Nylander-French LA, Parks CG, Chin H, et al. Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. Clin J Am Soc Nephrol. 2007;2(2):290-9.

32. Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ, et al. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. J Am Soc Nephrol. 2001;12(1):134-42.

33. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 2003;48(3):814-23.

34. Nuyts GD, Van Vlem E, De Vos A, Daelemans RA, Rorive G, Elseviers MM, et al. Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 1995;10(7):1162-5.

35. Stratta P, Messuerotti A, Canavese C, Coen M, Luccoli L, Bussolati B, et al. The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. Sci Total Environ. 2001;270(1-3):179-90.

36. Gourley M, Miller FW. Mechanisms of disease: Environmental factors in the pathogenesis of rheumatic disease. Nat Clin Pract Rheumatol. 2007;3(3):172-80.

37. Wahren-Herlenius M, Dorner T. Immunopathogenic mechanisms of systemic autoimmune disease. Lancet. 2013;382(9894):819-31.

38. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. J Autoimmun. 2007;29(1):1-9.

39. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. Lancet. 2013;382(9894):797-808.

40. Parks CG, Miller FW, Pollard KM, Selmi C, Germolec D, Joyce K, et al. Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease. Int J Mol Sci. 2014;15(8):14269-97.

41. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(10103):1685-99.

42. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108.

43. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. Lancet. 2014;384(9957):1878-88.

44. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013;17(5):603-6.

45. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol. 2005;19(2):191-207.

46. Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, et al. Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. J Autoimmun. 2012;39(4):272-84.

47. Maitre A, Hours M, Bonneterre V, Arnaud J, Arslan MT, Carpentier P, et al. Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. J Rheumatol. 2004;31(12):2395-401.

48. Flachs EM, Petersen SEB, Kolstad HA, Schlunssen V, Svendsen SW, Hansen J, et al. Cohort Profile: DOC*X: a nationwide Danish occupational cohort with eXposure data - an open research resource. Int J Epidemiol. 2019;48(5):1413-k.

49. ILO. ISCO, International Standard Classification of Occupations: International Labor Organisation; [Available from: https://www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm.

50. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011;39(7 Suppl):22-5.

51. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.

52. Peters S, Kromhout H, Portengen L, Olsson A, Kendzia B, Vincent R, et al. Sensitivity Analyses of Exposure Estimates from a Quantitative Job-exposure Matrix (SYN-JEM) for Use in Community-based Studies. Annals of Occupational Hygiene. 2013;57(1):98-106.

53. Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. Occup Environ Med. 2010;67(1):67-71.

54. Checkoway H, Pearce N, Hickey JL, Dement JM. Latency analysis in occupational epidemiology. Arch Environ Health. 1990;45(2):95-100.

55. Bondo Petersen S, Flachs EM, Prescott EIB, Tjønneland A, Osler M, Andersen I, et al. Job-exposure matrices addressing lifestyle to be applied in register-based occupational health studies. Occup Environ Med. 2018;75(1470-7926 (Electronic)):890-7.

56. BGIA. Report 8/2006e. Exposure to quartz at the workplace. Institute for Occupational Safety and Health; 2008.

57. HSE. MDHS 101/2, Chrystalline silica in respirable airborne dust. Health and Safety Executive,; 2014.

58. Hughes JP. Mixed effects models with censored data with application to HIV RNA levels. Biometrics. 1999;55(2):625-9.

59. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. 2019.

60. The European Parliament and Council of the European Union. Regulation (EC) No 1893/2006 of the European Parliament and of the Council of 20 December 2006 establishing the statistical classification of economic activities NACE Revision 2 and amending Council Regulation (EEC) 2006 [Available from: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32006R1893.

Bilag 1 Skriftlig videnskabelig formidling med peer review

International Journal of Epidemiology, 2021, 1–14
doi: 10.1093/ije/dyaa287
Original Article

Original Article

Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases: a nationwide cohort study

Signe Hjuler Boudigaard ,[1]* **Vivi Schlünssen,**[2,3]
Jesper Medom Vestergaard,[1] **Klaus Søndergaard,**[4] **Kjell Torén,**[5]
Susan Peters ,[6] **Hans Kromhout**[6] **and Henrik A Kolstad**[1]

[1]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Public Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark, [3]National Research Center for the Working Environment, Copenhagen, Denmark, [4]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [5]Occupational and Environmental Medicine, School of Public Health and Community Medicine, Sahlgrenska Academy, University of Goteborg, Goteborg, Sweden and [6]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

*Corresponding author.Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, 8210 Aarhus N, Denmark. E-mail: sigkrt@rm.dk

Received 4 September 2020; editorial decision 26 November 2020;

Abstract

Background: Exposure to respirable crystalline silica is suggested to increase the risk of autoimmune rheumatic diseases. We examined the association between respirable crystalline silica exposure and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis.

Methods: In a cohort study of the total Danish working population, we included 1 541 505 male and 1 470 769 female workers followed since entering the labour market 1979–2015. Each worker was annually assigned a level of respirable crystalline silica exposure estimated with a quantitative job exposure matrix. We identified cases of autoimmune rheumatic diseases in a national patient register and examined sex-specific exposure-response relations by cumulative exposure and other exposure metrics.

Results: We identified 4673 male and 12 268 female cases. Adjusted for age and calendar year, men exposed to high levels of respirable crystalline silica compared with non-exposed showed increased incidence rate ratio (IRR) for the four diseases combined of 1.53 [95% confidence interval (CI): 1.39–1.69], for systemic sclerosis of 1.62 (1.08–2.44) and rheumatoid arthritis of 1.57 (1.41–1.75). The overall risk increased with increasing cumulative exposure attained since entering the workforce [IRR: 1.07 (1.05–1.09) per 50 $\mu g/m^3$-years]. Female workers were less exposed to respirable crystalline silica, but showed comparable risk patterns with overall increased risk with increasing cumulative exposure [IRR: 1.04 (0.99–1.10) per 50 $\mu g/m^3$-years].

© The Author(s) 2021. Published by Oxford University Press on behalf of the International Epidemiological Association.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Conclusions: This study shows an exposure-dependent association between occupational exposure to respirable crystalline silica and autoimmune rheumatic diseases and thus suggests causal effects, most evident for systemic sclerosis and rheumatoid arthritis.

Key words: Respirable crystalline silica, autoimmune, systemic sclerosis, rheumatoid arthritis, cohort

Key Messages

- Inhalation of respirable crystalline silica has since the 1930s repeatedly been suggested in the aetiology of rheumatoid arthritis and other autoimmune rheumatic diseases.
- In a cohort of 3 million workers, we show an exposure-dependent association between respirable crystalline silica and systemic sclerosis, rheumatoid arthritis and possibly also systemic lupus erythematosus and small vessel vasculitis, supporting a causal role of this widespread occupational exposure.

Introduction

Crystalline silica (SiO_2) is a major element of earth's crust and found in soil, sand and rocks, and in concrete, ceramics, glass and other industrial materials. Worldwide, a considerable number of especially male workers employed in construction, the metal industry, farming and other industries are exposed at high levels, whenever these materials are used, moved, crushed, drilled in or processed in the production of new materials.[1,2] Since 1997, silica has been classified as a group 1 human lung carcinogen by the International Agency for Research on Cancer (IARC)[3] and inhalation of fine particles of silica is furthermore a well-recognized risk factor for silicosis.[4]

A causal link of rheumatic diseases with occupational exposure to crystalline silica was already suggested from the 1930s.[5] More recently, respirable crystalline silica has repeatedly been reported to increase the risk of several autoimmune rheumatic diseases: systemic sclerosis in men and women[6–9] and rheumatoid arthritis in men;[9–15] however, findings for women are unclear and based on few studies.[12,15] Exposure to respirable crystalline silica may also increase the risk of systemic lupus erythematosus[16–18] and small vessel vasculitis in men and women.[19–24] These diseases affect people of working age, women more often than men.[25–29] Low concordances between monozygotic twins indicate environmental factors as of aetiological importance.[30,31] Thus we have much to learn about the complex pathogenesis, which potentially includes interaction between genetic, environmental and epigenetic factors.[30,32]

Limited quantitative information on silica exposure levels characterizes most studies, and only few have examined exposure-response relations,[13,17,18,20] which are important before any conclusions on causation can be drawn. We combined a large and detailed nationwide occupational cohort with workplace surveillance exposure measurements, and examined the risk of systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis, following occupational exposure to respirable crystalline silica in men and women.

Methods

Register studies in Denmark without biological materials do not need approval from the National Committee of Health Research Ethics. This study is approved by the Danish Data Protection Agency (j.no: 1–16-02–196-17)

Study population

The study population comprised all Danish residents, born 1956 or later, with a minimum of 1 year of gainful employment 1977–2015 and a valid job code according to the Danish version of the International Standard Classification of Occupations from 1988 (ISCO 88) as registered in the Danish Occupational Cohort (DOC*X).[33] DOC*X includes annual, harmonized information on employment and job code for all Danish citizens. The information is based on several data sources, such as union membership, self-report to the civil registration authorities, tax records and employers' mandatory reporting of occupation to Statistics Denmark of all employees.[33] If the ISCO code was missing in a year with active employment, we assigned the latest valid ISCO code up to 5 years back. All Danish

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 1 Summary of the International Classification of Diseases (ICD) codes, 8th and 10th versions for the studied autoimmune rheumatic diseases

Disease	ICD 8 (1977–93)	ICD 10 (1994–2015)
Systemic sclerosis	73400, 73401, 73402, 73408, 73409, 73491	M34, M340, M341, M342, M342A, M342B, M348, M348B, M349
Rheumatoid arthritis	71219, 71229, 71238, 71239	M05, M050, M051, M051A-F, M052, M053, M058, M059, M06, M060, M068, M069
Seropositive rheumatoid arthritis[a]		M05, M050, M051, M051A-F, M052, M053, M058, M059
Seronegative rheumatoid arthritis[a]		M06, M060, M068, M069
Systemic lupus erythematosus	73419	M32, M320, M321, M328, M329
Small vessel vasculitis	22709, 44619, 44629, 44649, 44799, 44808, 44809	M301, M310, M310A-B, M311, M311A, M313, M317, M318, M318A, M319

[a]Rheumatoid arthritis is split into seropositive and seronegative rheumatoid arthritis in ICD 10.

citizens hold a unique social security number which is used by all official authorities and allows linkage with national registers. Through linkage with the national civil registration system'[4] we excluded those who died, disappeared or emigrated before the start of follow-up in 1979.

Autoimmune rheumatic diseases

Incident cases of autoimmune rheumatic diseases were identified in the National Patient Registry. Since 1977 the register holds information on all inpatient contacts and, since 1995, outpatient contacts with any Danish hospitals,[35] all coded according to the 8th (1977–93) or 10th (1994–2015) version of the International Classification of diseases. Cases were defined according to Table 1.

Exposure assessment

Each worker was assigned a quantitative estimate of respirable crystalline silica exposure for each year of employment, based on the SYNJEM job exposure matrix (JEM, developed for the SYNERGI study).[36,37] The SYNJEM originally provided time- and region-specific respirable crystalline silica exposure estimates for all job codes included in the 1968 version of ISCO, based on the modelling of 23 640 personal measurements of respirable crystalline silica from several European countries and Canada, together with expert assessments. For the current study, the SYNJEM was modified to provide exposure estimates for ISCO 88 job codes and was restricted to estimates for the Nordic countries. For each year of follow-up, we constructed the following exposure metrics based on each worker's exposure history since entry: (i) cumulative exposure (µg/m^3-year) as the sum of exposure levels for all exposed years; (ii) mean exposure intensity (µg/m^3) as cumulative exposure divided by the number of exposed years; (iii) highest attained exposure intensity (µg/m^3); and (iv) duration of exposure (years).

Statistical methods

Follow-up started the year following the first year of employment, because of no available information on month or day of employment. For the same reason, all independent variables were lagged by 1 year. We furthermore started follow-up at the earliest in 1979, 2 years after information on autoimmune rheumatic diseases was available from the National Patient Registry. We included this 2-year washout period (1977–78) to reduce number of prevalent cases. Study participants were followed until the year of the first diagnosis of systemic sclerosis, small vessel vasculitis, systemic lupus erythematosus or rheumatoid arthritis, death, emigration or end of follow-up on 31 December 2015, whichever came first.

Associations between respirable crystalline silica exposure and each of the autoimmune rheumatic diseases, as well as the studied diseases combined, were analysed in separate discrete time hazard models in a logistic regression procedure, with person-years as unit of analysis yielding incidence rate ratios that were presented with 95% confidence intervals (CI).[38] All exposures and covariates were treated as time-varying variables.

Table 2 presents the distribution of all male and female person-years cumulated during follow-up and classified by time worker characteristics and cumulative respirable crystalline silica exposure level. Separately for each exposure metric, study participants were grouped as exposed or non-exposed. The exposed were further grouped into tertiles based on the combined female and male distribution of exposed person-years. We also analysed respirable

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 2 Distribution of person-years at risk (%) by time-varying worker characteristics and cumulative respirable crystalline silica exposure level among 1 541 505 men and 1 470 769 women, Denmark, 1979–2015

	Men				Women			
	Cumulative respirable crystalline silica (μg/m³-years)				Cumulative respirable crystalline silica (μg/m³-years)			
Worker characteristics	0 28 596 448 Person-years	2.0–29.2 1 581 413 Person-years	29.3–93.9 1 644 508 Person-years	94.0–1622 1 790 255 Person-years	0 30 957 666 Person-years	2.0–29.2 342 405 Person-years	29.3–93.9 280 298 Person-years	94.0–1622 134 819 Person-years
Occupation[a]								
Armed forces	3	1	1	0	0	0	0	0
White-collar workers	40	17	13	12	63	36	32	29
Skilled blue-collar workers	17	26	28	41	1	12	14	21
Unskilled blue-collar workers	16	42	45	36	12	32	35	34
Others	12	13	10	7	14	18	16	12
Missing	12	1	3	4	10	2	3	4
Age								
<25	38	26	21	8	35	20	13	5
26–35	32	36	35	31	33	34	35	29
>36	29	38	44	61	32	46	52	66
Calendar year								
1979–84	7	2	6	2	6	2	3	1
1985–94	22	12	19	21	21	12	16	18
1995–2004	30	29	30	32	30	28	33	33
2005–15	41	57	45	45	43	58	48	48
Probability of smoking								
5–25%	24	23	18	21	35	37	29	28
26–35%	28	39	34	34	29	38	40	40
36–74%	32	38	48	45	24	25	31	32
Missing	16	–	–	–	12	–	–	–
Education[b]								
Lower secondary	27	43	44	30	26	38	40	41
Vocational or high secondary	46	44	45	61	44	43	45	46
Short cycle higher	5	3	3	3	3	4	4	4
Medium cycle higher	9	5	4	4	17	10	7	6
Long cycle higher	7	2	1	0	6	3	2	1
Unknown	6	3	3	2	4	2	2	2
Duration (year)								
0	100	0	0	0	100	0	0	0
1	0	58	4	0	0	60	3	0
2–5	0	41	68	13	0	40	72	20
6–39	0	1	28	87	0	0	25	80

[a]Grouped according to ISCO 88 = International Standard Classification of Occupations, 1988 revision: Armed forces (ISCO 88 codes 0110), White-collar workers (ISCO 88 codes 1000–5999), Skilled blue-collar workers (ISCO 88 codes 6000–7999), Unskilled blue-collar workers (ISCO 88 codes 8000–9999), Others (unemployed or retired).

[b]Highest attained educational level.

crystalline silica exposure accrued during three confined time windows (the previous 1–10, 11–20 and >20 years). In these analyses any silica exposure accrued outside each time window was classified as zero, and only exposure received in the years within the time windows were divided by the median into two exposure groups.[39]

All analyses were stratified by sex and adjusted for age (≤25, 26–35, ≥36 years), and calendar year of follow-up (1979-84, 1985–94, 1995–2004, 2005–15). We did not have information on smoking at an individual level, but in supplementary analyses we used a smoking JEM developed for the DOC*X cohort used in this study.[40] This JEM provided sex- and calendar year-specific estimates of smoking prevalence for all ISCO 88 job codes, based on self-reported smoking habits reported in four large Danish population-based surveys. Years without employment

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

were assigned the same smoking habit as in the latest job period. We furthermore conducted analyses adjusted for educational level (lower secondary, vocational or higher secondary, short-, medium- or long-cycle higher education, unknown) and analyses restricted to blue-collar workers (ISCO major categories 6–9) as defined at baseline, to obtain a more homogeneous population with respect to smoking and socioeconomic factors.

We analysed log-linear relations between respirable crystalline silica exposure and the autoimmune rheumatic diseases with continuous exposure variables. These analyses included the total study populations as well as the exposed populations only, with the low exposed as the reference. We fitted restricted cubic splines to the models, placing the knots at the 40, 60 and 80 percentiles. All analyses were carried out using Stata v.15 and v.16.

Results

The study population included 1 541 505 male workers cumulating 4673 cases of autoimmune rheumatic diseases during follow-up: systemic sclerosis ($n = 252$), rheumatoid arthritis ($n = 3490$), systemic lupus erythematosus ($n = 255$) and small vessel vasculitis ($n = 749$). The corresponding figures for 1 470 769 female workers were 12 268 cases of autoimmune rheumatic diseases: systemic sclerosis ($n = 746$), rheumatoid arthritis ($n = 9190$), systemic lupus erythematosus ($n = 1821$) and small vessel vasculitis ($n = 869$). Some participants were diagnosed with more than one autoimmune rheumatic disease and hence the number of specific diseases summed up to more than all autoimmune rheumatic diseases. Analyses for each disease were conducted separately and the respective study populations differed slightly. Only person-years at risk for the analyses of the studied autoimmune diseases combined are shown in the tables. The distribution of persons included in each exposure stratum is shown in Supplementary Table S3, available as Supplementary data at *IJE* online.

Among men, 17% ever held a job with exposure to respirable crystalline silica, and this was the case for 3% of the women. Furthermore, women were less exposed than men, with median cumulative exposure of 33 μg/m^3-years (25-75% centiles: 16-72 μg/m^3-years) versus 60 μg/m^3-years (23–135 μg/m^3-years) for men (Figure 1).

High exposure levels were associated with greater age, as expected, and with a higher probability of smoking (Table 2). There is an increasing time trend for being diagnosed with one of the studied autoimmune rheumatic diseases. In the time period 2005–15 compared with 1979–84, men had an increased risk (1.58, 95% CI: 1.30-1.92) of being diagnosed with one the studied diseases.

Among men, we observed an increased overall incidence rate ratio of the studied autoimmune rheumatic diseases combined of 1.53 (95% CI: 1.39-1.69) in analyses comparing the highest cumulative exposure stratum with non-exposure (Figure 2 and Table 3). Similar results were seen for mean exposure intensity, highest attained exposure intensity and duration of exposure. Furthermore, in the analysis of cumulative exposure, we observed an increasing trend of 1.07 (95% CI: 1.05-1.09) per 50 μg/m^3-years. The corresponding trend computed among the exposed only was 1.03 (95% CI: 1.00-1.05) per 50 μg/m^3-years. Similar risk patterns were seen for the respective diseases and most clearly for systemic sclerosis and rheumatoid arthritis. Cumulative exposure received more than 20 years earlier appears to be more influential for the exposure-response relation than cumulative exposure received more recently (Table 4).

Among women, we observed a slightly increased incidence rate ratio of 1.09 (95% CI: 0.87-1.37) for all the studied autoimmune rheumatic diseases combined, for the highest cumulative exposure stratum compared with no exposure, and a trend estimate of 1.04 (95% CI: 0.99-1.10) per 50 μg/m^3-years (Figure 2 and Table 3). Among women, there were also indications of a latency effect of more than 20 years; however, this was less evident than among men (Table 4).

In subanalyses of seropositive and seronegative rheumatoid arthritis (only possible for cases classified according to ICD 10), we observed an equally elevated incidence rate ratio for both serotypes in both sexes (Supplementary Table S1, available as Supplementary data at *IJE* online).

In additional analysis of men only, we added job-, sex-, and calendar year-specific estimates of smoking prevalence to the models, and observed an increased incidence rate ratio of 1.44 (95% CI: 1.31-1.59) for all autoimmune rheumatic disease when comparing high cumulative exposure with no exposure (Supplementary Table S2, available as Supplementary data at *IJE* online). In age-, calendar year- and education-adjusted analysis, comparing the highest cumulative exposed men with the unexposed, we observed a similar increased risk ratio of 1.37 (95% CI: 1.24-1.51). A sensitivity analysis restricted to male blue-collar workers showed an incidence rate ratio of 1.44 (95% CI: 1.31-1.59) for high versus no cumulative silica exposure (Supplementary Table S2).

Discussion

Principal findings

Among men, we observed increasing risk of autoimmune rheumatic diseases following increasing occupational exposure to respirable crystalline silica. Findings were

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

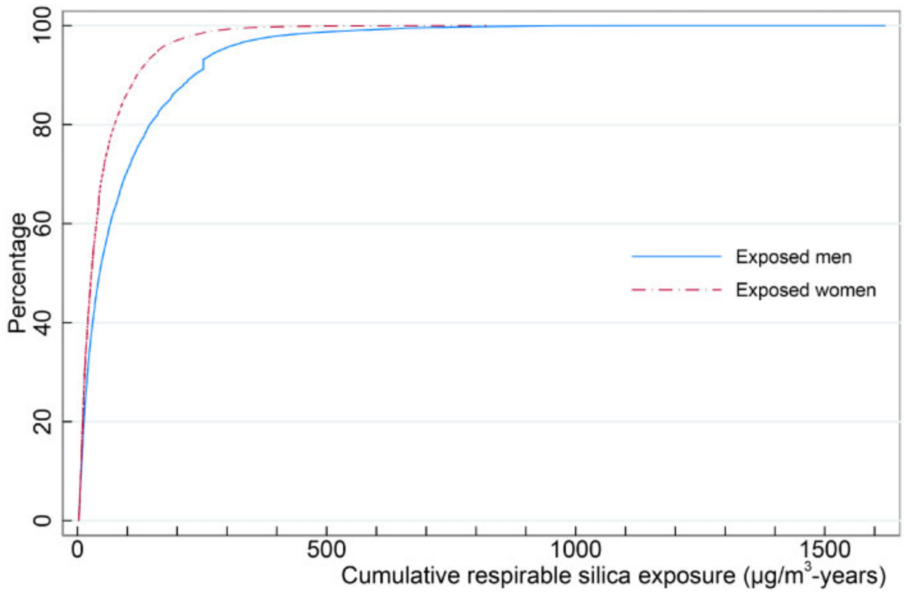


Figure 1 Cumulative plot of the distribution of cumulative exposure level ($\mu g/m^3$-years) at end of follow-up among 266 325 men and 42 914 women ever exposed to respirable crystalline silica

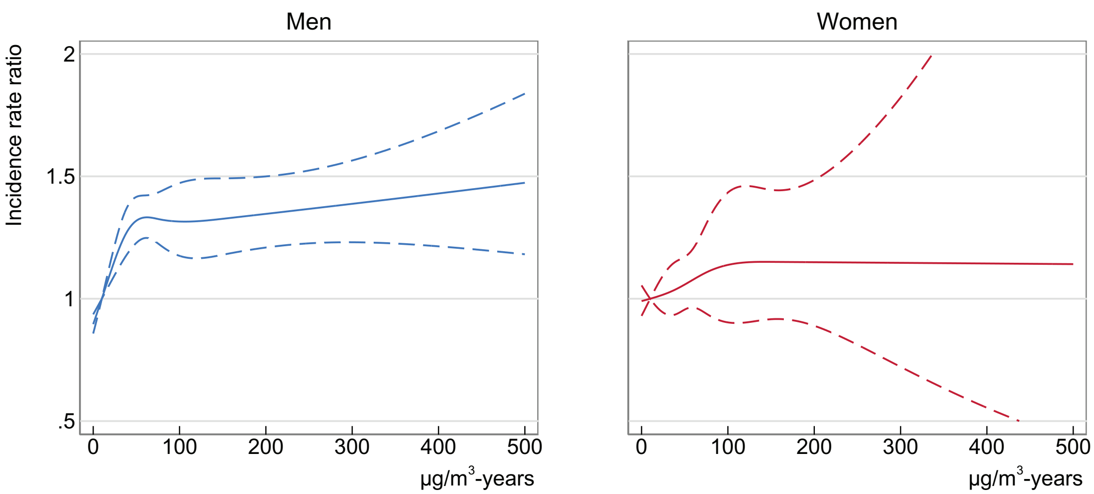


Figure 2 Restricted cubic spline fits of the age- and calendar year-adjusted overall incidence rate ratios of autoimmune rheumatic diseases by cumulated respirable crystalline silica among 1 541 505 men and 1 470 769 women, 1979–2015

strongest for systemic sclerosis and rheumatoid arthritis. Similar, but less evident, results were seen for women. However, few women were exposed at high levels.

Strengths and weaknesses of the study

The quantitative estimates of silica exposure based on job-exposure matrix derived from an extensive number of measurements allowed exposure response analyses, a prerequisite for causal inference. The long follow-up of a national working population combined with national health registers allowed us to study these rare diseases. However, the study still included a relatively limited number of exposed cases, especially few exposed female cases due to the rarity of silica exposure among women, and therefore the outcome still comes with considerable statistical uncertainty. The almost complete high coverage of the health registers precluded major selection bias. Information on occupation obtained from national labour marked registers, combined with exposure assessment based on a job exposure matrix, largely limited recall bias.

We identified cases in a national hospital register with positive predictive values of 79% for rheumatoid arthritis,[41] 94% for systemic sclerosis[42] and 73% for systemic

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 3. Incidence rate ratios (IRR) of the studied autoimmune rheumatic diseases combined, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis following exposure to respirable crystalline silica among 1 541 505 men and 1 470 769 women, Denmark, 1979–2015

Exposure	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)
Men											
Cumulative exposure (μg/m^3-years)											
0	28 527 938	3563	1	203	1	2630	1	198	1	587	1
2.0–29.2	1 576 698	283	1.23 (1.09–1.39)	8	0.69 (0.34–1.40)	218	1.24 (1.08–1.43)	18	1.42 (0.88–2.31)	46	1.34 (0.99–1.80)
29.3–93.9	1 639 692	351	1.42 (1.27–1.58)	14	1.04 (0.60–1.79)	267	1.42 (1.25–1.61)	16	1.22 (0.73–2.04)	57	1.54 (1.17–2.02)
94.0–1622	1 784 974	476	1.53 (1.39–1.69)	27	1.62 (1.08–2.44)	375	1.57 (1.41–1.75)	23	1.46 (0.94–2.27)	59	1.34 (1.02–1.76)
Per 50 μg/m^3-years			1.07 (1.05–1.09)		1.10 (1.03–1.18)		1.07 (1.05–1.10)		1.09 (1.01–1.17)		1.06 (1.01–1.11)
Per 50 μg/m^3-years (exposed only)			1.03 (1.00–1.05)		1.11 (1.02–1.21)		1.02 (0.99–1.05)		1.06 (0.96–1.18)		0.99 (0.93–1.07)
Mean exposure (μg/m^3)											
0	28 527 938	3563	1	203	1	2630	1	198	1	587	1
2.0–10.7	1 612 428	397	1.42 (1.28–1.57)	11	0.85 (0.46–1.57)	317	1.45 (1.29–1.63)	24	1.64 (1.06–2.52)	53	1.37 (1.03–1.83)
10.8–18.0	1 654 722	366	1.41 (1.26–1.57)	16	1.15 (0.69–1.92)	277	1.39 (1.23–1.58)	22	1.60 (1.03–2.50	58	1.55 (1.18–2.03)
18.1–122.0	1 734 214	347	1.39 (1.25–1.56)	22	1.46 (0.94–2.27)	266	1.43 (1.26–1.62)	11	0.84 (0.45–1.55)	51	1.30 (0.98–1.74)
Per 50 μg/m^3			2.27 (1.88–2.74)		1.90 (0.86–4.19)		2.34 (1.88–2.91)		1.57 (0.65–3.79)		2.27 (1.42–3.61)
Per 50 μg/m^3 (exposed only)			1.13 (0.75–1.70)		2.37 (0.44–12.72)		1.03 (0.65–1.65)		0.38 (0.48–2.93)		1.42 (0.50–4.04)
Highest attained exposure (μg/m^3)											
0	28 527 938	3563	1	203	1	2630	1	198	1	587	1
2.0–12.0	1 581 211	356	1.37 (1.23–1.53)	12	0.98 (0.55–1.77)	279	1.39 (1.22–1.57)	20	1.44 (0.90–2.28)	52	1.43 (1.07–1.91)
12.1–21.9	1 645 575	357	1.38 (1.24–1.55)	10	0.73 (0.39–1.38)	283	1.44 (1.27–1.62)	20	1.47 (0.93–2.33)	52	1.39 (1.04–1.84)
22.0–122	1 774 578	397	1.46 (1.31–1.62)	27	1.69 (1.12–2.54)	298	1.45 (1.29–1.64)	17	1.22 (0.74–2.01)	58	1.40 (1.06–1.84)
Per 50 μg/m^3			1.95 (1.69–2.25)		1.85 (1.02–3.39)		1.97 (1.68–2.32)		1.78 (0.93–3.40)		1.87 (1.29–2.70)
Per 50 μg/m^3 (exposed only)			1.29 (0.98–1.70)		2.62 (0.87–7.90)		1.20 (0.87–1.65)		1.41 (0.39–5.06)		1.20 (0.57–2.54)
Duration (years)											
0	28 527 938	3563	1	203	1	2630	1	198	1	587	1
1	974 370	145	1.09 (0.92–1.29)	6	0.84 (0.37–1.89)	108	1.08 (0.89–1.31)	9	1.24 (0.63–2.41)	23	1.11 (0.73–1.69)
2–5	1 993 555	395	1.38 (1.24–1.53)	14	0.90 (0.52–1.55)	304	1.41 (1.25–1.59)	21	1.36 (0.86–2.13)	65	1.48 (1.15–1.92)
6–39	2 003 439	570	1.54 (1.41–1.69)	29	1.54 (1.03–2.29)	448	1.56 (1.41–1.73)	27	1.44 (0.96–2.17)	74	1.46 (1.14–1.87)
Per 5 year			1.16 (1.13–1.20)		1.17 (1.02–1.35)		1.17 (1.13–1.21)		1.20 (1.04–1.37)		1.11 (1.02–1.22)
Per 5 year (exposed only)			1.07 (1.02–1.12)		1.21 (0.98–1.49)		1.07 (1.02–1.13)		1.15 (0.94–1.41)		0.97 (0.84–1.11)

(Continued)

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 3. Continued

Exposure	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	Cases	**IRR[c] (95% CI)**	Cases	**IRR[c] (95% CI)**	Cases	**IRR[c] (95% CI)**	Cases	**IRR[c] (95% CI)**	Cases	**IRR[c] (95% CI)**
					Women						
Cumulative exposure (μg/m^3-years)											
0	30 800 795	11 888	1	716	1	8906	1	1767	1	846	1
2.0–29.2	340 301	156	0.99 (0.84–1.16)	12	1.36 (0.77– 2.40)	114	0.93 (0.78– 1.12)	25	1.18 (0.79–1.75)	9	0.87 (0.45–1.69)
29.3–93.9	278 490	148	1.12 (0.95–1.31)	12	1.56 (0.88–2.76)	110	1.07 (0.88–1.29)	22	1.26 (0.83–1.93)	8	0.94 (0.47–1.88)
94.0–1622	133 920	76	1.09 (0.87–1.37)	6	1.46 (0.65–3.27)	60	1.10 (0.85–1.42)	7	0.82 (0.39–1.73)	6	1.38 (0.62–3.08)
Per 50 μg/m^3-years			1.04 (0.99–1.10)		1.14 (0.95–1.36)		1.05 (0.98–1.11)		1.04 (0.89–1.22)		1.03 (0.82–1.29)
Per 50 μg/m^3-years (exposed only)			1.03 (0.96–1.12)		1.04 (0.78–1.38)		1.05 (0.97–1.15)		0.98 (0.78–1.24)		1.10 (0.82–1.47)
Mean exposure (μg/m^3)											
0	30 800 795	11888	1	716	1	8906	1	1767	1	n.r.	1
2.0–10.7	300 872	149	0.96 (0.82–1.13)	7	0.86 (0.41–1.81)	113	0.92 (0.77–1.11)	20	1.01 (0.65–1.57)	n.r.	1.15 (0.63–2.08)
10.8–18.0	266 425	145	1.16 (0.99–1.37)	13	1.77 (1.02–3.07)	106	1.10 (0.91–1.33)	23	1.39 (0.92–2.10)	n.r.	0.99 (0.49–1.99)
18.1–122.0	185 414	86	1.07 (0.87–1.33)	10	1.92 (1.03–3.61)	65	1.07 (0.84–1.36)	11	1.01 (0.56–1.84)	n.r.	0.72 (0.27–1.93)
Per 50 μg/m^3			1.27 (0.91–1.77)		3.53 (1.28–9.74)		1.20 (0.82–1.75)		1.55 (0.66–3.65)		0.67 (0.16–2.87)
Per 50 μg/m^3 (exposed only)			1.42 (0.67–2.99)		5.05 (0.62–41.25)		1.60 (0.70–3.67)		1.42 (0.18–11.25)		0.37 (0.01–13.49)
Highest attained exposure (μg/m^3)											
0	30 800 795	11 888	1	716	1	8906	1	1767	1	846	1
2.0–12.0	333 072	167	0.99 (0.85–1.16)	8	0.90 (0.45–1.81)	127	0.97 (0.81–1.15)	22	1.01 (0.67–1.55)	12	1.15 (0.65–2.03)
12.1–21.9	257 420	129	1.08 (0.90–1.28)	12	1.69 (0.95–2.99)	97	1.05 (0.86–1.28)	19	1.19 (0.76–1.88)	6	0.77 (0.34–1.71)
22.0–122	162 219	84	1.16 (0.93–1.44)	10	2.15 (1.15–4.01)	60	1.08 (0.84–1.39)	13	1.36 (0.79–2.35)	5	1.01 (0.42–2.44)
Per 50 μg/m^3			1.23 (0.92–1.64)		2.90 (1.16–7.26)		1.16 (0.83–1.63)		1.46 (0.68–3.14)		0.84 (0.24–2.89)
Per 50 μg/m^3 (exposed only)			1.29 (0.68–2.45)		3.39 (0.46–24.96)		1.40 (0.68–2.89)		1.32 (0.22–7.93)		1.10 (0.07–17.82)
Duration (years)											
0	30 800 795	11 911	1	716	1	8906	1	1767	1	n.r.	1
1	210 515	93	1.00 (0.81–1.22)	10	1.86 (1.00–3.48)	70	0.98 (0.77–1.24)	11	0.86 (0.47–1.55)	n.r.	0.64 (0.24–1.72)
2–5	363 012	181	1.07 (0.93–1.24)	11	1.12 (0.62–-2.04)	130	1.00 (0.84–1.18)	32	1.42 (1.00–2.01)	n.r.	1.18 (0.68–2.04)
6–39	179 184	106	1.08 (0.89–1.31)	9	1.65 (0.85–3.18)	84	1.08 (0.87–1.34)	11	0.93 (0.51–1.69)	n.r.	1.01 (0.45–2.25)
Per 5 year			1.05 (0.97–1.14)		1.19 (0.89–1.59)		1.05 (0.95–1.15)		0.99 (0.77–1.28)		1.11 (0.81–1.51)
Per 5 year (exposed only)			1.03 (0.92–1.16)		0.99 (0.61–1.59)		1.05 (0.92–1.20)		0.82 (0.54–1.23)		1.24 (0.81–1.90)

n.r. not reported, cells with less than five cases.

[a]The studied diseases combined: systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and small vessel vasculitis.

[b]Number of person-years used for each analysis of the different outcomes differed slightly. Only total person-years from the analysis of all autoimmune rheumatic disease combined are shown in the tables.

[c]Adjusted for age (≤25, 26–35,≥36) and calendar year (1979–84, 1985–94, 1995–2004, 2005–15).

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 4 Incidence rate ratios (IRR) of the studied autoimmune rheumatic diseases combined, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis following respirable crystalline silica exposure accrued during the previous 1–10, 11–20 and >20 years time windows among 1 541 505 men and 1 470 769 women, Denmark, 1979–2015

	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
Exposure	Person-years[b]	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)
					Men						
Cumulative exposure (μg/m^3-years)											
1–10 years											
0	29 829 503	3975	1	217	1	2953	1	217	1	650	1
2.0–37.1	1 779 056	355	1.36 (1.22–1.51)	19	1.45 (0.90–2.31)	271	1.36 (1.20–1.54)	18	1.26 (0.78–2.04)	55	1.38 (1.05–1.82)
37.2–875.2	1 920 743	343	1.30 (1.16–1.45)	16	1.02 (0.61–1.70)	266	1.36 (1.20–1.55)	20	1.37 (0.86–2.17)	44	1.03 (0.76–1.41)
Per 50 μg/m^3-years			1.10 (1.04–1.16)		1.07 (0.87–1.31)		1.12 (1.06–1.19)		1.14(0.93–1.39)		1.00 (0.87–1.16)
11–20 years	31 276 025	4038	1	222	1	2986	1	223	1	668	1
03.5–47.6	1 081 784	302	1.42 (1.27–1.60)	16	1.64 (0.98–2.75)	227	1.36 (1.19–1.56)	15	1.40 (0.82–2.37)	51	1.80 (1.35–2.41)
47.7–875.2	1 171 493	333	1.46 (1.30–1.63)	14	1.27 (0.73–2.20)	277	1.54 (1.36–1.75)	17	1.54 (0.93–2.55)	30	1.00 (0.69–1.45)
Per 50 μg/m^3-years			1.13 (1.08–1.18)		1.16 (0.97–1.38)		1.14 (1.09–1.20)		1.14 (0.94–1.37)		1.01 (0.88–1.16)
>20 years											
0	32 434 659	4242	1	230	1	3153	1	236	1	689	1
6.1–66.6	521 145	184	1.42 (1.23–1.66)	7	1.28 (0.59–2.75)	145	1.40 (1.18–1.66)	10	1.72 (0.90–3.29)	25	1.52 (1.01–2.29)
66.7–1338.5	573 498	247	1.70 (1.49–1.94)	15	2.48(1.44–4.27)	192	1.65 (1.42–1.92)	9	1.37 (0.69–2.71)	35	1.87 (1.32–2.66)
Per 50 μg/m^3-years			1.13 (1.10–1.17)		1.22 (1.09–1.36)		1.12 (1.08–1.16)		1.15 (1.00–1.32)		1.17 (1.08–1.26)
Mean exposure (μg/m^3)											
1–10 years											
0	29 829 503	3975	1	217	1	2953	1	217	1	650	1
0.1–9.2	1 836 924	490	1.42 (1.29–1.56)	22	1.43 (0.91–2.23)	392	1.45 (1.30–1.61)	217	1.77 (1.13–2.49)	56	1.19 (0.90–1.57)
9.3–122.0	1 862 875	208	1.15 (1.00–1.33)	13	0.97 (0.55–1.72)	145	1.17 (0.99–1.39)	29	0.77 (0.39–1.52)	43	1.22 (0.89–1.67)
Per 50 μg/m^3			1.77 (1.24–2.53)		1.09 (0.28–4.17)		1.96 (1.26–3.04)	9	1.20 (0.25–5.76)		1.57 (0.73–3.38)
11–20 years											
0	31 276 025	4038	1	222	1	2986	1	223	1	668	1
0.1–8.1	1 148 078	373	1.56 (1.40–1.74))	20	2.45 (1.55–3.87)	292	1.55 (1.37–1.75)	23	1.95 (1.26–3.03)	45	1.40 (1.03–1.91)
8.2–110	1 105 199	262	1.30 (1.15–1.48))	10	1.27 (0.68–2.40)	212	1.34 (1.16–1.54)	9	0.90 (0.46–1.76)	36	1.38 (0.98–1.95)
Per 50 μg/m^3			2.72 (1.90–3.88)		1.76 (0.32–9.54)		2.90 (1.95–4.32)		2.02 (0.38–10.63)		2.49 (0.92–6.76)
>20 years											
0	32 434 659	4242	1	230	1	3153	1	236	1	689	1
0.2–11.7	561 913	184	1.56 (1.36–1.80)	14	2.37 (1.36–4.15)	170	1.54 (1.31–1.80)	10	1.61 (0.84–3.08)	26	1.48 (0.99–2.21)
11.8–110	532 730	247	1.58 (1.37–1.81)	8	1.41 (0.69–2.91)	167	1.53 (1.31–1.80)	9	1.46 (0.74–2.88)	34	1.93 (1.35–2.76)
Per 50 μg/m^3			2.95 (2.19–3.98)		4.86 (1.37–17.24)		2.74 (1.95–3.85)		1.94 (0.41–9.18)		4.06 (1.88–8.74)
Highest attained exposure (μg/m^3)											
1–10 years											
0	29 829 503	3975	1	217	1	2953	1	217	1	650	1
2.0–12.5	1 776 923	441	1.41 (1.28–1.56)	15	1.05 (0.62–1.78)	352	1.45 (1.30–1.62)	23	1.41 (0.92–2.18)	60	1.38 (1.05–1.80)
12.6–121.9	1 922 876	257	1.21 (1.06–1.37)	20	1.39 (0.87–2.21)	185	1.23 (1.05–1.42)	15	1.19 (0.70–2.03)	39	1.01 (0.72–1.40)
Per 50 μg/m^3			1.91 (1.48–2.46)		1.69 (0.66–4.31)		2.08 (1.54–2.82)		1.78 (0.62–5.15)		1.40 (0.76–2.59)

(Continued)

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 4 Continued

Exposure	The studied diseases combined[a] Person-years[b]	Cases	IRR[c] (95% CI)	Systemic sclerosis Cases	IRR[c] (95% CI)	Rheumatoid arthritis Cases	IRR[c] (95% CI)	Systemic lupus erythematosus Cases	IRR[c] (95% CI)	Small vessel vasculitis Cases	IRR[c] (95% CI)
11–20 years											
0	31 276 025	4038	1	222	1	2986	1	223	1	668	1
3.5–15.8	1 047 317	352	1.56 (1.39–1.74)	13	1.30 (0.74–2.31)	279	1.55 (1.37–1.76)	21	1.92 (1.21–3.04)	50	1.68 (1.25–2.27)
15.9–121.9	1 205 960	282	1.32 (1.17–1.49)	17	1.58 (0.95–2.61)	225	1.35 (1.18–1.55)	11	1.02 (0.55–1.88)	31	1.09 (0.76–1.57)
Per 50 μg/m^3			2.10 (1.72–2.57)		2.17 (0.91–5.00)		2.18 (1.74–2.74)		2.13 (0.89–5.11)		1.62 (0.91–2.89)
>20 years											
0	32 434 659	4242	1	230	1	3153	1	236	1	689	1
6.1–23.4	504 415	207	1.60 (1.39–1.84)	8	1.49 (0.72–3.08)	164	1.59 (1.35–1.86)	10	1.71 (0.89–3.27)	30	1.80 (1.23–2.62)
23.5–121.9	590 228	224	1.54 (1.34–1.77)	14	2.26 (1.29–3.95)	173	1.49 (1.27–1.74)	9	1.38 (0.70–2.73)	30	1.63 (1.12–2.37)
Per 50 μg/m^3			2.04 (1.71–2.44)		2.97 (1.41–6.25)		1.95 (1.60–2.39)		1.85 (0.77–4.42)		2.26 (1.40–3.66)
					Women						
Cumulative exposure (μg/m^3-years)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	854	1
2.0–37.1	319 807	134	0.98 (0.82–1.16)	10	1.26 (0.68–2.36)	93	0.89 (0.72–1.09)	24	1.23 (0.82–1.83)	10	1.08 (0.58–2.02)
37.2–875.2	182 463	68	0.97 (0.76–1.23)	5	1.08 (0.45–2.61)	52	1.00 (0.76–1.31)	7	0.65 (0.31–1.36)	5	1.00 (0.41–2.40)
Per 50 μg/m^3-years			1.00 (0.87–1.15)		0.92 (0.52–1.63)		1.00 (0.85–1.19		0.96 (0.67–1.38)		0.99 (0.60–1.65)
11–20 years											
0	31 252 372	12 085	1	732	1	9050	1	1798	1	n.r.	1
3.5–47.6	194 665	118	1.09 (0.91–1.31)	9	1.54 (0.79–2.97)	88	1.02 (0.83–1.26)	15	1.14 (0.69–1.90)	n.r.	1.40 (0.73–2.71)
47.7–875.2	106 469	65	1.08 (0.84–1.38)	5	1.51 (0.62–3.64)	52	1.08 (0.82–1.42)	8	1.14 (0.57–2.29)	n.r.	0.58 (0.14–2.31)
Per 50 μg/m^3-years			1.03 (0.92–1.16)		1.16 (0.75–1.77)		1.02 (0.89–1.17)		1.06 (0.76–1.48)		0.96 (0.56–1.65)
>20 year											
0	31 417 074	12 150	1	736	1	9096	1	n.r	1	n.r.	1
6.1–66.6	92 154	79	1.27 (1.01–1.58)	5	1.48 (0.61–3.57)	62	1.22 (0.95–1.57)	n.r	1.91 (1.08–3.38)	n.r.	1.09 (0.41–2.93)
66.7–1338.5	44 278	39	1.30 (0.95–1.78)	5	3.06 (1.27–7.40)	32	1.31 (0.92–1.85)	n.r	0.66 (0.17–2.65)	n.r.	1.69 (0.54–5.27)
Per 50 μg/m^3-years			1.12 (1.02–1.24)		1.36 (1.06–1.74)		1.14 (1.02–1.26)		1.15 (0.86–1.53)		1.13 (0.77–1.66)
Mean exposure (μg/m^3)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	n.r.	1
0.1–9.2	261 915	129	0.94 (0.82–1.16)	8	1.11 (0.55–2.23)	97	0.90 (0.74–1.10)	14	0.81 (0.478–1.37)	n.r.	1.57 (0.91–2.72)
9.3–122.0	240 355	73	1.03 (0.76–1.23)	7	1.31 (0.62–2.77)	48	0.98 (0.73–1.30)	17	1.30 (0.81–2.11)	n.r.	0.34 (0.08–1.35)
Per 50 μg/m^3			0.78 (0.39–1.55)		2.18 (0.31–15.40)		0.65 (0.28–1.54)		0.99 (0.21–4.57)		0.19 (0.1–3.64)
11–20 years											
0	31 252 372	12 085	1	n.r.	1	9050	1	1798	1	n.r.	1
0.1–8.1	128 933	83	1.11 (0.89–1.37)	5	1.23 (0.51–2.96)	65	1.09 (0.85–1.39)	10	1.14 (0.61–2.12)	858	0.33 (0.60–2.98)
8.2–110	172 201	100	1.07 (0.88–1.30)	9	1.77 (0.91–3.42)	75	1.01 (0.80–1.27)	13	1.14 (0.66–1.98)	6	0.93 (0.38–2.24)
Per 50 μg/m^3			1.24 (0.68–2.26)		5.37 (0.93–31.02)		1.03 (0.51–2.07)		1.30 (0.24–6.87)	5	0.28 (0.11–15.32)

(Continued)

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Table 4 Continued

Exposure	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)
>20 years											
0	31 417 074	12 150	1	n.r.	1	9096	1	1807	1	n.r.	1
0.2–11.7	54 240	50	1.37 (1.04–1.81)	n.r.	2.03 (0.76–5.43)	39	1.31 (0.96–1.80)	5	1.36 (0.56–3.28)	n.r.	1.89 (0.70–5.05)
11.8–110	82 192	68	1.21 (0.95–1.54)	n.r.	1.97 (0.88–4.42)	55	1.20 (0.92–1.57)	9	1.60 (0.83–3.09)	n.r.	0.91 (0.29–2.82)
Per 50 µg/m^3			1.91 (1.14–3.20)		4.79 (0.94–24.47)		1.95 (1.11–3.44)		3.30 (0.84–12.98)		1.11 (0.10–12.74)
Highest attained exposure (µg/m^3)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	n.r.	1
2.0–12.5	311 925	148	0.97 (0.82–1.14)	9	1.10 (0.57–2.13)	109	0.91 (0.76–1.10)	20	0.99 (0.64–1.54)	n.r.	1.38 (0.79–2.38)
12.6–121.9	190 345	54	0.98 (0.75–1.29)	6	1.37 (0.61–3.08)	36	0.96 (0.69–1.34)	11	1.08 (0.59–1.95)	n.r.	0.42 (0.10–1.68)
Per 50 µg/m^3			0.83 (0.47–1.46)		1.63 (0.28–9.42)		0.73 (0.37–1.46)		0.93 (0.25–3.49)		0.40 (0.04–3.54)
11–20 years											
0	31 252 372	12 085	1	732	1	9050	1	1798	1	n.r.	1
3.5–15.8	183 189	114	1.04 (0.87–1.25)	8	1.37 (0.68–2.76)	87	0.99 (0.80–1.23)	15	1.19 (0.72–1.99)	n.r.	1.08 (0.51–2.28)
15.9–121.9	117 945	69	1.17 (0.92–1.48)	6	1.80 (0.80–4.02)	53	1.14 (0.87–1.49)	8	1.05 (0.53–2.11)	n.r.	1.17 (0.44–3.13)
Per 50 µg/m^3			1.29 (0.84–1.97)		2.90 (0.69–12.27)		1.18 (0.72–1.93)		1.62 (0.52–5.01)		1.26 (0.22–7.36)
>20 years											
0	31 417 074	12 150	1	n.r.	1	9096	1	1807	1	n.r.	1
6.1–23.4	84 633	73	1.26 (1.00–1.58)	n.r.	1.27 (0.47–3.40)	60	1.27 (0.98–1.64)	9	1.55 (0.80–2.99)	n.r.	1.16 (0.43–3.12)
23.5–121.9	51 799	45	1.31 (0.97–1.75)	n.r.	3.22 (1.44–7.21)	34	1.21 (0.86–1.70)	5	1.43 (0.59–3.45)	n.r.	1.50 (0.48–4.69)
Per 50 µg/m^3			1.66 (1.12–2.46)		4.13 (1.19–14.32)		1.62 (1.04–2.51)		2.52 (0.85–7.45)		1.75 (0.35–8.74)

n.r. not reported, cells with less than five cases.

[a]The studied diseases combined: systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis .

[b]Number of person-years used for each analysis of the different outcomes differed slightly. Only total person-years from the analysis of all autoimmune rheumatic disease combined are shown in the tables.

[c]Adjusted for age (≤25, 26–35, ≥36) and calendar year (1979–84, 1985–94, 1995–2004, 2005–15).

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

lupus erythematosus, when compared with medical records as the gold standard.[43] Thus false-positive cases, except perhaps for systemic sclerosis, may have biased measures of association most likely towards the null.

Smoking is a well-documented risk factor for rheumatoid arthritis and probably also for systemic lupus erythematosus[44,45] and could have confounded our risk estimates, as could other factors related to social class. However, we still observed increased risks of the studied diseases when adjusting by: estimates of smoking prevalence via a smoking JEM; highest attained educational level; and in analyses restricted to blue-collar workers expected to have fairly comparable life style patterns across different occupations and silica exposure levels.

Comparison with other studies

Our results are in line with extensive evidence linking occupational exposure to respirable crystalline silica and autoimmune rheumatic diseases.[44–46] To our knowledge, only few studies have examined the association with quantitative exposure levels.[12,13] Vihlborg *et al.*[13] observed a doubled risk of seropositive rheumatoid arthritis of [standardized incidence ratio of 2.59 (95% CI: 1.24-4.76)] at exposure levels of respirable crystalline silica above 50 $\mu g/m^3$ and exposure-response relation in a cohort of male foundry workers. Others have observed increasing risk with increasing duration of exposure and semi-quantified exposure levels (never, low, high).[6,8,17,18,20] Turner *et al.*[12] did not, however, observe an association between quantitative levels of silica exposure and rheumatoid arthritis in a cohort of pottery, sandstone and refractory material workers.

Whereas the prevalence of autoimmune rheumatic diseases is higher among women, the association with respirable crystalline silica exposure is most evident among men in our study, most likely because fewer women were exposed and when exposed their cumulative exposure was lower. Exposure-response patterns were similar for men and women though.

In a meta-analysis by Rubio-Rivas *et al.* of respirable crystalline silica exposure and systemic sclerosis, they found a slightly higher risk among men than women.[47] Similarly, the risk of rheumatoid arthritis among men was slightly higher than the risk for men and women combined in a meta-analysis by Khuder *et al.*[48] A single study on systemic lupus erythematosus found a higher risk among men than among women.[18] However, an animal model with male and female lupus-prone mice did not demonstrate sex-related differences in outcomes after exposure to crystalline silica.[49]

We observed increased risks of several of the studied autoimmune rheumatic diseases at mean exposure intensity levels well below the current European occupational exposure limit of 100 $\mu g/m^3$,[50] indicating that this limit provides insufficient protection of workers exposed to crystalline silica.

Possible mechanisms

Following inhalation, respirable crystalline silica particles are deposited in the alveoli.[1] Animal models have shown that macrophages phagocyte the particles, activating the immune system by secretion of cytokines, chemokines and lysosomal enzymes, which activate antigen-presenting and in turn antibody-producing cells.[46,51] In susceptible individuals, a disturbed control mechanism and breaking of tolerance result in continuous production of auto-antibodies.[32,51] Apoptosis of macrophages results in release of silica particles and new uptake by antigen-presenting cells, contributing to chronic inflammation.[46] For silicosis it has been shown that most of the disease progression takes place after termination of exposure to crystalline silica.[52] Retained silica in lung tissue, and other similar or partly overlapping mechanisms as for silicosis, may explain the increased risks observed in this study more than 20 years after exposure. Furthermore, auto-antibodies are present years before clinical symptoms of systemic lupus erythematosus develop,[53,54] and it has been suggested that triggering exposures in susceptible individuals first lead to serological autoimmunity and later to overt clinical disease.[32] This could also explain the highest risks we observed following exposure accrued more than 20 years earlier.

Conclusions

This study shows an exposure-dependent association between respirable crystalline silica, systemic sclerosis and rheumatoid arthritis, and possibly also systemic lupus erythematosus and small vessel vasculitis. Findings were most evident in men, but few women were exposed at high levels.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

This work was supported by a grant from the Danish Working Environment Research Fund (grant no. 34–2016-09). SP and HK received a grant from the Deutsche Gesetzliche Unfallversicherung to elaborate SYNJEM.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

Acknowledgements

The authors would like to thank Lützen Portengen for help with understanding and interpretation of the statistical methods used.

Conflicts of interest

None declared.

References

1. Roney N, Faroon O, Williams M *et al. Toxicological Profile for Silica*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service: Agency for Toxic Substances and Disease Registry (ATSDR), 2019.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Arsenic, Metals, Fibres, and Dusts*. Lyon, France: IARC, 2012.
3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils*. Lyon, France: IARC, 1997.
4. T Mannetje A, Steenland K, Attfield M *et al.* Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med* 2002;**59**: 723–28.
5. Collis EL, Gu Y. The mortality experience of an occupational group exposed to silica dust, compared with that of the general population and an occupational group exposed to dust not containing silica. *J Indust Hyg* 1933;**15**:395–417.
6. Diot E, Lesire V, Guilmot JL *et al.* Systemic sclerosis and occupational risk factors: a case-control study. *Occup Environ Med* 2002;**59**:545–49.
7. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Male systemic sclerosis and occupational silica exposure - a population-based study. *Aust N Z J Med* 2000;**30**: 215–20.
8. Marie I, Gehanno JF, Bubenheim M *et al.* Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014;**13**:151–56.
9. Blanc PD, Jarvholm B, Toren K. Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers. *Am J Med* 2015;**128**:1094–101.
10. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940-81. *Br Med J (Clin Res Ed)* 1987;**294**:997–1000.
11. Stolt P, Yahya A, Bengtsson C *et al.*; the EIRA Study Group. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:1072–76.
12. Turner S, Cherry N. Rheumatoid arthritis in workers exposed to silica in the pottery industry. *Occup Environ Med* 2000;**57**: 443–47.
13. Vihlborg P, Bryngelsson IL, Andersson L, Graff P. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. *BMJ Open* 2017;**7**:e016839.
14. Yahya A, Bengtsson C, Larsson P *et al.* Silica exposure is associated with an increased risk of developing ACPA-positive rheumatoid arthritis in an Asian population: evidence from the Malaysian MyEIRA case-control study. *Mod Rheumatol* 2014; **24**(2):271–74
15. Ilar A, Alfredsson L, Wiebert P, Klareskog L, Bengtsson C. Occupation and risk of developing rheumatoid arthritis: results from a population-based case-control study. *Arthritis Care Res* 2018;**70**:499–509.
16. Cooper GS, Wither J, Bernatsky S; CaNIOS GenES Investigators *et al.* Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. *Rheumatology (Oxf)* 2010;**49**:2172–80.
17. Finckh A, Cooper GS, Chibnik LB *et al.* Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. *Arthritis Rheum* 2006;**54**:3648–54.
18. Parks CG, Cooper GS, Nylander-French LA *et al.* Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. *Arthritis Rheum* 2002;**46**: 1840–50.
19. Gregorini G, Ferioli A, Donato F *et al.* Association between silica exposure and necrotizing crescentic glomerulonephritis with P-Anca and Anti-Mpo antibodies - a hospital-based case-control study. *Anca-Associated Vasculitides* 1993;**336**:435–40.
20. Hogan SL, Cooper GS, Savitz DA *et al.* Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. *CJASN* 2007;**2**:290–99.
21. Hogan SL, Satterly KK, Dooley MA *et al.* Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. *J Am Soc Nephrol* 2001;**12**:134–42.
22. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study. *Arthritis Rheum* 2003;**48**:814–23.
23. Nuyts GD, Van Vlem E, De Vos A *et al.* Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. *Nephrol Dial Transplant* 1995;**10**:1162–65.
24. Stratta P, Messuerotti A, Canavese C *et al.* The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. *Sci Total Environ* 2001;**270**:179–90.
25. Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;**390**: 1685–99.
26. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;**376**:1094–108.
27. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet* 2014;**384**:1878–88.
28. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol* 2013;**17**:603–06.
29. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? *Best Pract Res Clin Rheumatol* 2005; **19**:191–207.
30. Gourley M, Miller FW. Mechanisms of disease: Environmental factors in the pathogenesis of rheumatic disease. *Nat Rev Rheumatol* 2007;**3**:172–80.
31. Selmi C, Leung PS, Sherr DH *et al.* Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. *J Autoimmun* 2012;**39**:272–84.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

32. Wahren-Herlenius M, Dorner T. Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet* 2013;**382**:819–31.
33. Flachs EM, Petersen SEB, Kolstad HA *et al.* Cohort Profile: DOCX: a nationwide Danish occupational cohort with eXposure data—an open research resource. *Int J Epidemiol* 2019;**48**:1413–k.
34. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–25.
35. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90.
36. Peters S, Kromhout H, Portengen L *et al.* Sensitivity Analyses of Exposure Estimates from a Quantitative Job-exposure Matrix (SYN-JEM) for use in community-based studies. *Ann Occup Hyg* 2013;**57**:98–106.
37. Peters S, Vermeulen R, Portengen L *et al.* Modelling of occupational respirable crystalline silica exposure for quantitative exposure assessment in community-based case-control studies. *J Environ Monit* 2011;**13**:3262–68.
38. Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. *Occup Environ Med* 2010;**67**:67–71.
39. Checkoway H, Pearce N, Hickey JL, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health* 1990;**45**:95–100.
40. Bondo Petersen S, Flachs EM, Prescott EIB *et al.* Job-exposure matrices addressing lifestyle to be applied in register-based occupational health studies. *Occup Environ Med* 2018;**75**:890–97.
41. Ibfelt EH, Sorensen J, Jensen DV *et al.* Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. *Clin Epidemiol* 2017;**9**:627–32.
42. Butt SA, Jeppesen JL, Fuchs C *et al.* Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: a nationwide cohort study. *BMC Rheumatol* 2018;**2**:36.
43. Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of systemic lupus erythematosus and lupus nephritis in Denmark: a nationwide cohort study. *J Rheumatol* 2016;**43**:1335–39.
44. Miller FW, Alfredsson L, Costenbader KH *et al.* Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. *J Autoimmun* 2012;**39**:259–71.
45. Parks CG, Miller FW, Pollard KM *et al.* Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease. *Int J Mol Sci* 2014;**15**:14269–97.
46. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. *Int Immunopharmacol* 2002;**2**:303–13.
47. Rubio-Rivas M, Moreno R, Corbella X. Occupational and environmental scleroderma. Systematic review and meta-analysis. *Clin Rheumatol* 2017;**36**:569–82.
48. Khuder SA, Peshimam AZ, Agraharam S. Environmental risk factors for rheumatoid arthritis. *Rev Environ Health* 2002;**17**:307–15.
49. Brown JM, Archer AJ, Pfau JC, Holian A. Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice. *Clin Exp Immunol* 2003;**131**:415–21.
50. European Parliament and the Council of the European Union, Official Journal of the European Union (L 345/87). DIRECTIVE (EU) 2017/2398 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Brussels: European Parliament and the Council of the European Union, 2017.
51. Pollard KM. Silica, silicosis, and autoimmunity. *Front Immunol* 2016;**7**:97.
52. Miller BG, Hagen S, Love RG *et al.* Risks of silicosis in coalworkers exposed to unusual concentrations of respirable quartz. *Occup Environ Med* 1998;**55**:52–58.
53. Eriksson C, Kokkonen H, Johansson M, Hallmans G, Wadell G, Rantapää-Dahlqvist S. Autoantibodies predate the onset of systemic lupus erythematosus in northern Sweden. *Arthritis Res Ther* 2011;**13**:R30.
54. Rantapää-Dahlqvist S, de Jong BAW, Berglin E *et al.* Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:2741–49.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa287/6104043 by Hospitalsenhed Midt user on 25 January 2021

International Journal of Epidemiology, 2021, 1–4
doi: 10.1093/ije/dyab133
Letters to the Editor

Authors' response to: Occupational exposure to respirable crystalline silica and autoimmunity: sex-differences in mouse models

Signe Hjuler Boudigaard ,[1] Vivi Schlünssen,[2,3] Jesper Medom Vestergaard,[1] Klaus Søndergaard,[4] Kjell Torén,[5] Susan Peters ,[6] Hans Kromhout[6] and Henrik A Kolstad[1]*

[1]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Public Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark, [3]National Research Center for the Working Environment, Copenhagen, Denmark, [4]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [5]Occupational and Environmental Medicine, School of Public Health and Community Medicine, Sahlgrenska Academy, University of Goteborg, Goteborg, Sweden and [6]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

*Corresponding author. Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark. E-mail: kolstad@clin.au.dk

Accepted 15 June 2021

We thank Lescoat *et al.*[1] for their interest in our recent article reporting positive exposure response relations between quantitative measures of occupational exposure to respirable crystalline silica and incidence of autoimmune rheumatic diseases in men and in women.[2] We are grateful for the new experimental and mechanistic evidence they present which shed important light on the possible mechanisms behind our epidemiological findings.

Our results suggest a less evident exposure response relation for women than for men. Lescoat *et al.* propose that this reflects a sex-dependent effect. They refer to experimental data supporting this interpretation.

In response to Lescoat *et al.*, we searched the literature for articles presenting separate estimates for men and for women of the association between silica exposure and autoimmune rheumatic diseases. We identified seven additional studies, which assessed exposure differently from our study, i.e. largely based on occupational history combined with expert assessment and self-reports and not based on quantitative model estimates as was ours. Furthermore, all but one included few participants. We computed relative odds ratios for women versus men for each study and corresponding relative incidence rate ratios for our own published results. As can be seen from Table 1, the relative ratio estimates indicated no disease-specific pattern by sex.

We also analysed our combined dataset of men and women and included sex as an interaction term in the adjusted models of cumulative exposure (the principal exposure metric). The interaction term represents the log of the relative incidence rate ratio for women compared with men. After exponentiation, we found relative incidence rate ratio estimates very close to those computed from the published sex-specific estimates: 1.03 [95% confidence interval (CI) 0.85-1.25), 0.98 (95% CI 0.91-1.04), 0.98 (95% CI 0.82-1.16) and 0.97 (95% CI 0.77-1.23) for systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis, respectively.

In conclusion, these additional analyses indicate a less evident association between silica exposure and rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis for women than for men, whereas the opposite was suggested for systemic sclerosis. However, estimates were given with considerable uncertainty and earlier studies provided no support for sex-specific effects. Thus, there is still much to learn about possible sex-dependent effects of these diseases that dominate among women.

Funding

This work was supported by a grant from the Danish Working Environment Research Fund (grant no. 34–2016-09). SP and HK received a grant from the Deutsche Gesetzliche Unfallversicherung to elaborate SYNJEM.

Conflict of interest

None declared.

References

1. Lescoat A, Ballerie A, Lecureur V. Occupational exposure to respirable crystalline silica and autoimmunity: sex differences in mouse models, International Journal of Epidemiology. 2021 doi: 10.1093/ije/dyab125.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab133/6314894 by Aarhus University Library user on 18 August 2021

Table 1 Summary of eight studies providing sex-specific association between exposure to crystalline silica and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis

Study, country	Study population (cases/controls by sex)	Exposure assessment	Outcome	Confounders accounted for	Odds ratios (95% CI)[a] Women	Odds ratios (95% CI)[a] Men	Relative odds or rate ratios (95% CI)
Systemic sclerosis							
Diot *et al.*, 2002 France[3]	General population, F: 69/138 M: 11/22	Occupational history combined with blinded expert assessment and self-reported silica exposures	Medical records, ACR criteria	Age, smoking	13.04 (1.54-110.66)	3.62 (0.64-20.40)	3.60 (0.23-56.36)
Bovenzi *et al.*, 2003 Italy[4]	General population, F: 46/153 M: 9/18	Occupational history combined with blinded expert assessment and self-reported silica exposures	Medical records, ACR criteria	Age	2.4 (0.4-15.5)	1.2 (0.1-15.8)	2.00 (0.08-45.41)
Maître *et al.*, 2004 France[5]	General population, F: 83/166 M: 10/40	Occupational history combined with blinded expert assessment and self-reported silica exposures	Disease register ACR criteria	Age, education	No exposed cases	0.9 (0.2-4.4)	–
Marie *et al.*, 2014 France[6]	General population, F: 22/66 M: 78/234	Occupational history combined with blinded expert assessment and self-reported silica exposures	Medical records, ACR criteria	Smoking	3.08 (0.40-23.49)	8.30 (2.58-29.60)	0.37 (0.03-3.99)
Boudigaard *et al.*, 2021[2]	General working population, F: 746/1 470 618[b] M: 252/1 541 416[b]	Lifelong occupational history combined with quantitative JEM	National health registries, ICD-8 and ICD-10	Age, calendar year	1.14 (0.95–1.36)[c]	1.10 (1.03–1.18[c]	1.04 (0.86-1.26)
Rheumatoid arthritis							
Turner *et al.*, 2000 UK[7]	Pottery and sandstone workers, F: 15/60 M: 43/172	Occupational history within potteries combined with industry-specific JEM	Diagnoses from medical surveillance scheme	Smoking, parity (women), coal mining employment (men)	1.13 (0.73-1.73) [d]	0.71 (0.52-0.97) [d]	1.59 (0.93-2.71)

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab133/6314894 by Aarhus University Library user on 18 August 2021

Table . (continued)

Study, country	Study population (cases/controls by sex)	Exposure assessment	Outcome	Confounders accounted for	Odds ratios (95% CI)[a]		Relative odds or rate ratios (95% CI)
					Women	Men	
Ilar *et al.*, 2019 Sweden[8]	General population, F: 7622/77 902 M: 3634/37 064	Occupational titles from national census combined with JEM	National health registries, ICD-10	Age, county, calendar year	1.2 (0.9-1.6)	1.6 (1.4-1.7)	0.75 (0.55-1.03)
Boudigaard *et al.*, 2021 Denmark[2]	General working population, F: 9190/1 470 129[b] M: 3490/1 541 217[b]	Lifelong occupational history combined with quantitative JEM	National health registries, ICD-8 and ICD-10	Age, calendar year	1.05 (0.98–1.11)[c]	1.07 (1.05–1.10)[c]	0.98 (0.92- 1.05)
Systemic lupus erythematosus							
Parks *et al.*, 2002 USA[9]	General population, F: 240/321 M: 25/34	Occupational history combined with blinded expert assessment and self-reported specific exposures	Medical records, ACR criteria	Age, state, race, education	3.3 (0.6-17.8)[e]	6.0 (0.7-48.0)[e]	0.55 (0.04-8.26)
Boudigaard *et al.*, 2021 Denmark[2]	General working population F: 1821/1 470 559[b] M: 255/1 541 465[b]	Lifelong occupational history combined with quantitative JEM	National health registries, ICD-8 and ICD-10	Age, calendar year	1.04 (0.89–1.22)[c]	1.09 (1.01–1.17)[c]	0.95 (0.80-1.14)
Small vessel vasculitis							
Boudigaard *et al.*, 2021 Denmark[2]	General working population F: 869/1 469 392[b] M: 749/1 539 809[b]	Lifelong occupational history combined with quantitative JEM	National health registries, ICD-8 and ICD-10	Age, calendar year	1.03 (0.82–1.29)[c]	1.06 (1.01–1.11)[c]	0.97 (0.77-1.23)

JEM, job exposure matrix; F, female; M, male; ICD-8, 8th version of the International Classification of Diseases; ICD-10, 10th version of the International Classification of Diseases; ACR criteria, American College of Rheumatology classification criteria; CI, confidence interval.

[a]Odds ratio for ever vs never silica exposure unless else stated.

[b]Persons at risk.

[c]Rate ratio per 50 $\mu g/m^3$-years.

[d]Odds ratio per 1000 $\mu g/m^3$-years.

[e]Odds ratio for high vs no silica exposure.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab133/6314894 by Aarhus University Library user on 18 August 2021

2. Boudigaard SH, Schlünssen V, Vestergaard JM *et al.* Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases: a nationwide cohort study. *Int J Epidemiol*. 2002 doi: 10.1093/ije/dyaa287
3. Diot E, Lesire V, Guilmot JL *et al.* Systemic sclerosis and occupational risk factors: a case-control study. *Occup Environ Med* 2002;**59**:545–49.
4. Bovenzi M, Barbone F, Pisa FE *et al.* A case-control study of occupational exposures and systemic sclerosis. *Int Arch Occup Environ Health* 2004;**77**:10–16.
5. Maitre A, Hours M, Bonneterre V *et al.* Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. *J Rheumatol* 2004;**31**:2395–401.
6. Marie I, Gehanno JF, Bubenheim M *et al.* Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014;**13**:151–56.
7. Turner S, Cherry N. Rheumatoid arthritis in workers exposed to silica in the pottery industry. *Occup Environ Med* 2000;**57**:443–47.
8. Ilar A, Klareskog L, Saevarsdottir S *et al.* Occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study. *RMD Open* 2019;**5**:e000978.
9. Parks CG, Conrad K, Cooper GS. Occupational exposure to crystalline silica and autoimmune disease. *Environ Health Perspect* 1999;**107(Suppl 5)**:793–802.

Downloaded from https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyab133/6314894 by Aarhus University Library user on 18 August 2021

Annals of Work Exposures and Health, 2021, 1–9, Vol. XX, No. XX
https://doi.org/10.1093/annweh/wxab116
Original Article

The Chartered Society for Worker Health Protection
OXFORD

Original Article

Determinants of Respirable Quartz Exposure Concentrations Across Occupations in Denmark, 2018

Signe Hjuler Boudigaard[1,*], Karoline Kærgaard Hansen[1], Henrik Kolstad[1,2], Hans Kromhout[3] and Vivi Schlünssen[4,5]

[1]Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, 8200 Aarhus N, Denmark; [2]Institute of Clinical Medicine, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, 8200 Aarhus N, Denmark; [3]Department of Population Health Sciences, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Yalelaan 2, 3584 CM Utrecht, The Netherlands; [4]Department of Public Health, Environment, Work and Health, Danish Ramazzini Centre, Aarhus University, Bartholins Alle 2, bg. 1260, 8000 Aarhus C, Denmark; [5]National Research Center for the Working Environment, Lersø Parkallé 125, 2100 Copenhagen, Denmark

*Author to whom correspondence should be addressed. Tel: +45-78-45-09-00; e-mail: sigkrt@rm.dk.

Submitted 24 September 2021; revised 19 November 2021; editorial decision 19 November 2021; revised version accepted 5 December 2021.

Abstract

Background: High concentrations of respirable quartz have been reported from workers in construction, foundries, and quarries. Current exposure concentrations in prevalent but presumably lower exposed occupations have been less examined. We aimed to quantify current exposure concentrations of respirable dust and quartz across prevalent occupations and to identify determinants of respirable quartz exposure across these occupations.

Methods: One hundred and eighty-nine full-shift personal samples of respirable dust of workers within 11 occupations in Denmark were sampled during 2018. Respirable dust was determined gravimetrically and analysed for quartz content with infrared spectrometry. Determinants for respirable quartz exposure, i.e. use of power tools, outdoor or indoor location, and percentage of quartz in respirable dust, were analysed in linear mixed effect models.

Results: The overall geometric means (geometric standard deviations) for respirable dust and quartz were 216 µg m^{-3} (4.42) and 16 µg m^{-3} (4.07), respectively. The highest quartz concentrations were observed among stone cutters and carvers [93 µg m^{-3} (3.47)], and metal melters and casters [61 µg m^{-3} (1.71)]. Use of power tools increased exposure concentrations of quartz by a factor of 3.5. Occupations explained 27%, companies within occupations 28%, and differences between workers within companies within occupations 14% of the variability in quartz concentrations. Thirty percent was due to day-to-day variability in exposure concentrations. In total, 19% of the variation in quartz

© The Author(s) 2021. Published by Oxford University Press on behalf of the British Occupational Hygiene Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

concentration could be explained by type of tool, indoor/outdoor location, and percentage of quartz in respirable dust.

Conclusion: Current exposure concentrations are generally low, but some occupations in this study had average exposure concentrations to respirable quartz above the ACGIH threshold limit value of 25 µg m^{-3}. Preventive measures to lower excess risk of quartz-related diseases among these workers are still needed. In terms of preventive strategies, use of power tools and quartz content of used materials were identified as main determinants of exposure. Lowering of exposures will be most efficient when focussed on these major determinants, e.g. tool dust control with water, dust extraction, and use of low quartz content materials.

Keywords: determinants of exposure; exposure variability; mixed effect model; occupational exposure; quartz exposure; respirable dust; silica exposure; work place measurements

What's Important About This Paper?

Exposure to respirable quartz is a well-documented workplace hazard in some highly exposed occupations. However, exposure concentrations in a number of prevalent, but less-exposed jobs are not well described. This study measures quartz exposure levels across a number of occupations and examine determinants for exposure concentrations together with variance components within and between workers, occupations, and companies. The study adds important knowledge to be used in preventive strategies.

Background

Crystalline silica is present in most rocks and is a major constituent of sand and soil. Alpha-quartz is the most abundant of several forms of crystalline silica (IOM, 2011; IARC, 2012). The general population is exposed to low levels of airborne crystalline silica through outdoor and indoor sources, for example resuspension of settled dust indoors, and silica-containing commercial products (i.e. cosmetics, cleansers, pet litter, putty, and paint) (IARC, 2012; Roney *et al.*, 2019). Workers in agriculture, construction, mining, quarrying, and manufacturing of metal products may be exposed to high concentrations of respirable silica (Peters *et al.*, 2011; IARC, 2012). Respirable crystalline silica exposure is a well-documented risk factor for silicosis (t Mannetje *et al.*, 2002) and lung cancer (IARC, 2012; Ge *et al.*, 2020) and is associated with the occurrence of rheumatoid arthritis, systemic sclerosis, and other autoimmune rheumatic diseases (Miller *et al.*, 2012; Boudigaard *et al.*, 2021).

In general, exposure concentrations of respirable crystalline silica have declined over the past 50 years (Yassin *et al.*, 2005; Creely *et al.*, 2007; Peters *et al.*, 2011; Zilaout *et al.*, 2020), but high concentrations are still reported in foundries (Andersson *et al.*, 2009; Radnoff *et al.*, 2014), the stone and brick sector (Healy *et al.*, 2014; Radnoff *et al.*, 2014; Baldwin *et al.*, 2019), and in construction (Radnoff *et al.*, 2014; Bello *et al.*, 2019). It was estimated that 5.3 million workers in Europe were potentially occupationally exposed to respirable crystalline silica in 2006, of which 75% were employed in construction (IOM, 2011). However, not all construction workers are exposed to high concentrations (Hammond *et al.*, 2016). To implement an efficient preventive strategy, knowledge on exposure concentrations in prevalent, but less-exposed jobs are warranted in addition to the known high exposed jobs.

The aim of the present study is to quantify current exposure concentrations of respirable quartz and to identify determinants of exposure across occupations.

Materials and methods

Companies and participants

Based on the prevalence of occupations in Denmark with expected quartz exposure (BGIA, 2008; Peters *et al.*, 2011; IARC, 2012), we identified companies employing construction-, metal-, and concrete workers and farmers. Occupations were classified based on the four-digit level of the Danish version of the International Standard Classification of Occupations, ISCO-88 (ILO, 2004). Industry was classified at two-digit level of the European classification of industries, NACE vers.2 (The European Parliament and Council of the European Union, 2006) (Table 1, Supplementary Table S1). We prioritized inclusion of companies of different sizes, and when feasible companies with employees from more than one relevant occupation located in the eastern part of Jutland. A total

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

Table 1. Characteristics, respirable dust and respirable quartz (μg m^{-3}) among 140 persons, Denmark, 2018

Characteristics	Persons	Samples	Respirable dust		Quartz		Respirable dust μg m^{-3}			Quartz μg m^{-3}			% of quartz in respirable dust	Quartz μg m^{-3} (>LOD) min–max	Exceedance (%)[c]
	K	N	<LOD[a]	%	<LOD[b]	%	AM	GM	GSD	AM	GM	GSD			
Occupational group (ISCO88)															
7113. Stonecutters and carvers	10	15	0	0	0	0	1224	534	3.44	199	93	3.47	18	20–1083	48
7122. Bricklayers and stonemason	17	24	3	13	9	38	260	86	5.32	57	21	4.36	30	10–194	15
7123. Concrete placers, finishers and related	16	23	1	4	12	52	152	114	2.30	14	8	1.92	14	9–56	<1
7129. Building frame and related trades workers	21	21	0	0	3	14	1554	741	2.83	57	34	2.95	7	9–179	16
7220. Blacksmiths, tool-makers and related	9	11	0	0	7	64	1038	718	2.50	21	9	4.78	9	25–121	6
8112. Mineral, ore or stone processing-plant operators	8	11	0	0	3	27	304	185	3.00	39	22	4.06	17	11–196	14
8122. Metal melters, casters and rolling-mill operators	10	18	0	0	0	0	1032	719	1.97	69	61	1.71	11	24–165	18
8131. Glass, ceramics kiln and related machine operators	17	22	0	0	10	45	394	297	2.27	21	12	2.26	6	10–58	1
8212. Cement/other mineral products machine operators	7	11	0	0	8	73	196	176	1.55	13	5	1.72	7	9–22	<1
8332. Earth-moving- and related plant operators	10	14	5	36	10	71	41	25	2.57	10	4	2.95	19	10–14	<1
9310. Mining and construction labourers	15	19	1	5	9	47	154	94	2.88	18	10	2.49	17	10–71	1
Industry (NACE, rev.2)															
8. Other mining and quarrying	10	14	0	0	3	21	337	209	2.90	41	22	3.41	16	11–196	11
23. Manufacture of other non-metallic mineral products	34	48	0	0	18	38	597	311	2.69	72	20	4.81	10	9–1083	15
24. Manufacture of basic metals	10	18	0	0	0	0	1032	746	1.97	69	60	1.71	11	24–165	17
25. Manufacture of fabricated metal products, except machinery and equipment	7	8	0	0	7	88	1200	888	2.45	13	3	3.75	8	25–25	<1
41. Construction of buildings	7	14	1	7	11	79	136	88	2.73	16	5	3.85	25	11–55	1
42. Civil engineering	16	21	0	0	12	57	169	111	2.48	19	8	3.11	16	10–71	1
43. Specialized construction activities	56	66	9	14	20	30	688	153	6.68	42	18	3.58	16	9–194	9
Tool															
None	15	19	0	0	11	58	424	254	2.47	19	8	2.40	8	9–58	<1
Use of hand tools	44	72	4	6	32	44	398	197	3.98	33	15	3.82	17	10–165	8
Use of power tools	40	46	0	0	8	17	1224	462	4.15	90	30	4.36	13	9–1083	21
Operating construction machines	41	52	6	12	20	38	287	110	4.37	26	13	3.27	16	9–196	4
Location															
Indoor	68	93	0	0	27	29	916	478	2.78	62	23	3.82	10	9–776	14
Outdoor	72	96	10	10	44	46	309	100	4.33	30	12	4.11	19	9–1083	6
Total	140	189	10	5	71	38	604	216	4.42	46	16	4.07	15	9–1083	10

[a]LOD for respirable dust = 24 μg m^{-3}.
[b]LOD for respirable quartz = 9 μg m^{-3}.
[c]Exceedance of OEL 100 μg m^{-3}.

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

of 38 companies were approached; 15 large companies with more than 100 employees and 23 small companies with less than 100 employees. In total 24 companies (63%) agreed to participate of which 5 employed workers from more than one relevant occupation. Sixty percent of the large companies and 65% of the small companies accepted the invitation. Farmers were contacted through a farmers' trade associations; however, no farmers were recruited.

Managers at the worksites were instructed to select up to eight employees with work tasks representative for the targeted occupations.

Sampling and analytical method

On the measurement day, participants filled in a questionnaire about primary task, tools, or construction machines used, whether their work location was indoor or outdoor, and use of a respirator. We conducted full-shift measurements; however, pumps were turned off during breaks lasting more than 15 min. Measurements with sampling time below 4 h were excluded. All companies were asked to participate in a second measuring round. If they agreed, repeated measurements were carried out on study participants who remained at the worksite. All measurements were carried out by the same technician between April and December 2018.

Respirable dust was collected on 25-mm PVC filters using a conductive plastic sampler with a respirable dust cyclone (SKC LTD conductive plastic cyclone) connected to SKC AirChek XR5000 portable pump (SKC Inc., Eighty-Four, PA) calibrated at a flow rate of 2.2 l/min. The cassette was attached to the upper part of the participant's chest within the breathing zone.

Respirable dust was determined gravimetrically. Filters were conditioned for a minimum of 24 h (22°C, 45% relative humidity) before weighing using a Mettler UMT2 analytical scale (Mettler-Toledo Ltd, Greifensee, Switzerland) with 0.1-mg precision. One field blank was included per visit (n = 45). The lower limit of detection (LOD) for respirable dust was calculated as three times the Standard deviation (SD) of the weight changes of the field blanks, corresponding to a concentration of 24 µg m^{-3}, when assuming 8-h measurements.

Quartz was determined by Fourier transform infrared spectrometry, in accordance with MDHS 101/2 (HSE, 2014). The analytical level of quantification for quartz was 10 µg, assuming 8-h measurements correspond to a concentration of 9 µg m^{-3}.

Statistical analysis

Respirable dust and respirable quartz concentrations were log normally distributed, assuming values below LOD followed the same distribution. Hence, statistical analyses were performed using log-transformed values. We used mixed effects Tobit models (metobit, Stata) for interval censored data. All left censored values (values below LOD) were assumed to be in an interval between (-∞) and the LOD (Hughes, 1999; StataCorp., 2019).

In the applied mixed effect models, worker, company, and occupation were included as random effects, and tool, location, and percentage of quartz in respirable dust as fixed effects. β-coefficients are displayed as Exp β with 95% confidence intervals (CI). Geometric standard deviation factor (GSD) was calculated as $\exp\left(\sqrt{\sigma^2_{wY} + \sigma^2_{bY}}\right)$, where σ^2_{wY}= within-worker variance and σ^2_{bY} = between-worker variance. The occupational exposure limit (OEL) in Denmark and several European countries is 100 µg m^{-3} (The European Parliament and Council of the European Union, 2017), and we calculated the exceedance fraction above as $P\left[Z > \frac{\ln(OEL)-\ln(GM)}{\ln(GSD)}\right]$.

If an occupational group was represented by less than 10 persons on ISCO-88 major group 4 level, it was merged with similar occupations on the corresponding ISCO-88 major group 3 level. Tool was categorized into no tool, hand tools, power tools, and operating construction machines. Location was dichotomized into primarily working inside or outside (Table 1, Supplementary Table S1). The percentage of quartz in respirable dust was imputed for quartz measurements below LOD (38%). For the majority of missing values, we used the median of the percentage of quartz from other workers doing the same job at the same company. For the remaining seven missing values, where none of the co-workers had detectable values of quartz, we used the median percentage from all workers in the same job and company using the estimated LOD value of quartz.

All analyses were carried out using Stata, version 16 and 17.

Results

We performed 194 measurements on 143 participants. One measurement was lost during transportation and four with a sampling time of less than 4 h did not fulfil our inclusion criteria and were excluded, leaving 189 measurements from 140 participants for further analyses. The median sampling time was 428 min, with an interquartile range of 367–456 min. Repeated measurements were available for 35% of the participants, with a median duration between the two measurements of 91 days, interquartile range 84–125 days.

All together 15% of workers (21 participants) reported use of respirators at some point during the day, with

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

missing information from 5% of the measurements. For nine participants using respirators, quartz concentrations were below the LOD, and the range in concentrations among workers using respirators was from 11 to 1083 μg m^{-3}. The majority (68%) of the respirator users reported using power tools, 45% were employed in a large company (<100 employees), and 55% in a smaller company.

Five percent of the respirable dust measurements and 38% of the quartz measurements were below LOD (Table 1). Thirteen percent of all measurements were above the OEL. Measured quartz concentrations ranged from values <LOD to 1083 μg m^{-3}. Stone cutters and carvers were the only occupation having measurements with concentrations above 200 μg m^{-3} and had a probability of exceedance of 48%. Construction workers (bricklayers, stonemasons, and other building frame workers), mineral or stone processing-plant operators, and metal melters and casters had lower quartz concentrations and probability of exceedance between 14 and 18% (Table 1).

The geometric mean, GM (geometric standard deviation, GSD) for respirable dust exposure concentration was 216 μg m^{-3} (4.42). Highest exposure concentrations were found among demolition workers and scaffolding fitters (included in the building frame workers category), with a GM of 741 μg m^{-3} (2.83), metal melters and casters with a GM of 719 μg m^{-3} (1.97), and blacksmiths with a GM of 718 μg m^{-3} (2.50) (Table 1).

The GM (GSD) of overall quartz exposure concentration was 16 μg m^{-3} (4.07). Highest concentrations were observed among stonecutters and carvers, GM of 93 μg m^{-3} (3.47), and metal melters and casters, GM of 61 μg m^{-3} (1.71) (Table 1). Percentage of quartz in respirable dust varied from 6 to 30% across occupations. Highest percentage were seen among bricklayers and stonemasons (Table 1).

Use of hand or power tools compared with no tools increased quartz exposure concentrations, e.g. use of power tools resulted in a 3.5 times higher exposure [exp(β) = 3.46 (1.66–7.21)] (Table 2). The quartz content was also an important determinant, with 3 percentage increase in quartz exposure concentration for each percent increase in quartz content in respirable dust.

Of the total variance, occupations explained 27%, companies within occupations 29%, and workers within a company within an occupation 14% of the variability in quartz concentrations. Thirty percent was due to day-to-day variability in quartz concentrations. Including tool and location as fixed effects into the model explained 13% of the total variability, primarily decreasing the variability between workers within companies and occupations (35% explained). When percentage of quartz in respirable dust was added, the fixed effects explained 19% of the total variability, 38% of the variability between occupations, 14% between companies within occupation, and 29% between workers within companies and occupations (Table 3).

Discussion

Based on 189 measurements, respirable dust and quartz exposure concentrations was generally low across the 11 sampled occupations, but a few occupations had high average concentration. Furthermore, a number of the measurements showed quartz concentrations well above the OEL. Use of power tools and quartz percentage in respirable dust were the most important determinants of quartz exposure concentrations and explained much of the variability in quartz concentrations between companies and between workers within companies and occupations.

We have included several prevalent, moderately to highly exposed occupations. However, the size of the sample limits the number of occupations and persons within each occupation, potentially affecting the accuracy of the estimated exposure concentrations. The exposure concentrations found in our study are generally in line with concentrations observed in similar occupations, if reported yearly decreasing exposure trends are taken into account (Yassin *et al.*, 2005; Creely *et al.*, 2007; Peters *et al.*, 2011; Zilaout *et al.*, 2020). In our study, metal melters and casters are among the highest quartz exposed occupations, and our results indicate slightly lower exposure concentrations compared with results from iron foundries in Sweden from 2005, where the authors reported overall exposure concentrations (GM) of respirable quartz of 280 μg m^{-3} (Andersson *et al.*, 2009). Compared with our results, slightly lower exposure concentrations from the non-ferrous foundry industry in Canada were reported, with GM of 25 μg m^{-3} from 2009 to 2013 (Radnoff *et al.*, 2014).

Compared with earlier studies of construction workers (Rappaport *et al.*, 2003; Tjoe Nij *et al.*, 2004; Peters *et al.*, 2011; Radnoff *et al.*, 2014; van Deurssen *et al.*, 2014; Baldwin *et al.*, 2019; Bello *et al.*, 2019), we find similar or lower quartz concentrations. Measurements from 2009 to 2013 in Canadian construction workers showed a GM of respirable quartz of 105 μg m^{-3} among bricklayer and concrete finisher (Radnoff *et al.*, 2014). Our study shows comparable exposure concentrations with those reported in SYNJEM for bricklayers (GM average of 30 μg m^{-3} across Europe and Canada in 1998, ranging from 20 to 70 μg m^{-3}) and from a study of bricklayers in the Netherlands in 2014 (20 μg m^{-3}) (van Deurssen *et al.*, 2014).

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

Table 2. Determinants of respirable quartz concentration (µg m^{-3}), 189 personal measurements among 140 workers, Denmark, 2018

	Exp (β)	95 % CI	*P*-value
Model including fixed effects: Occupation, company, and worker as random effects, tool and location as fixed effects			
Intercept	6.66	2.80–15.81	<0.001
Tool			
None (REF)	1		
Use of hand tools	2.20	1.04–4.65	0.038
Use of power tools	3.51	1.66–7.41	0.001
Operating construction machines	1.82	0.87–3.82	0.114
Location			
Indoor	1.21	0.69–2.12	0.511
Outdoor (REF)	1		
Model including fixed effects: Occupation, company and worker as random effects, and tool, location and content of quartz in dust as fixed effects			
Intercept	4.12	1.65–10.25	0.002
Tool			
None (REF)	1		
Use of hand tools	2.18	1.05–4.53	0.036
Use of power tools	3.46	1.66–7.21	0.001
Operating construction machines	1.76	0.85–3.64	0.127
Location			
Indoor	1.40	0.79–2.46	0.250
Outdoor (REF)	1		
Content of quartz in respirable dust			
Per 1% increase in quartz content	1.03	1.01–1.05	0.010

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

Table 3. Variance components for respirable quartz level from models excluding and including fixed effects

	Model excluding fixed effects	Model including tool and location as fixed effects	% explained	Model including tool, location and the content of quartz in dust as fixed effects	% explained
Between-occupation variance	0.53	0.45	15	0.33	38
Between-company variance	0.56	0.46	17	0.48	14
Between-worker variance	0.28	0.18	35	0.20	29
Within-worker variance	0.60	0.63	−5	0.58	3
Total variance	1.97	1.72	13	1.59	19

If companies with low dust exposure concentrations were more inclined to participate in the study, the observed exposure concentrations would underestimate the true exposure levels. In Denmark, companies decide how to monitor the working environment, but they have to comply with the occupational exposure limit (OEL) for silica and dust. Quantitative monitoring (measurements) is not routinely performed by the working environment authority. Hence, it is possible that larger companies with a working environment organization and regularly dust exposure monitoring would be more prone to participate in this study. We tried to take this potential selection bias into account by recruiting both small and large companies, and they have similar participation rates, 65 and 60%, respectively. The selection of the sampled workers by managers might have biased the results, but given that we selected the jobs and the (unpredictable) large day-to-day variability in exposure concentrations we consider this bias to be minimal.

Self-reported information on indoor vs. outdoor location and tool used could be misclassified. However, since the workers are unaware of exposure concentration to respirable quartz, this should be non-differential and would primarily attenuate the shown effect of location and tool.

The use of SKC LTD plastic cyclone has potentially resulted in oversampling of respirable quartz (Verpaele and Jouret, 2013). In the mixed effect model, the potential oversampling should have no effect on modelling determinants of exposure and estimation of the variance components.

Approximately one third of all quartz measurements were below LOD. This has to be taken into account in accepting the assumption of log normality. Furthermore, how these very small values are treated will highly effect the GM (Hewett and Ganser, 2007). Due to high numbers of values below LOD in our study, we refrained from imputation of the left censored values. Instead, we used a Tobit model that takes the distribution probability of the missing values into account. We assume that this should not have a major effect on comparability of mean exposure concentrations with studies using imputation techniques. We did however impute the percentage of quartz, when quartz and/or respirable dust was below the LOD. When we restricted the analysis to measurements above LOD as expected more variability in exposure concentrations was explained (55% of total variability, results not shown).

Use of power tools and percentage of quartz are the main determinants for increased quartz exposure

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

concentrations. The effect of power tools corresponds well with findings from other studies among construction workers (Healy *et al*., 2014; Baldwin *et al*., 2019). Percentage of quartz in dust reflects the material used and explains some of the difference in exposure concentrations between occupations. Hence, in terms of preventive strategies, control measures for power tools (e.g. tool dust control with water and dust extraction) and substitution of materials with high quartz content will lower quartz exposure concentrations, as well as reducing differences between occupations and to a lesser extend companies.

Conclusion

Even though exposure concentrations in 2018 across many occupations in Denmark generally are low, some prevalent occupations had average exposure concentrations to respirable quartz above the ACGIH threshold limit value of 25 µg m^{-3}. Preventive measures to lower excess risk of diseases among these workers are still needed. In terms of preventive strategies, use of power tools and quartz content of materials worked with were identified as main determinants of exposure. Lowering of exposures will be most efficient when focused on these major determinants.

Supplementary data

Supplementary data are available at *Annals of Work Exposures and Health* online.

Funding

This work was supported by a grant from the Danish Working Environment Research Fund (grant no.34-2016-09).

Acknowledgements

The authors wish to thank the participating companies and workers for contributing to this research, and statistician Morten Frydenberg for valuable contribution in statistical analysis of data.

Conflict of interest

HKr receives funding from the Industrial Minerals Association Europe for maintaining and analysing exposure data from their Dust Monitoring Programme (https://www.ima-europe.eu/commitments/dust-monitoring-programme). The authors declare no other conflict of interest relating to the material presented in this paper. Its contents, including any opinions and/or conclusions expressed, are solely those of the authors.

Data availability

The data underlying this paper cannot be shared publicly due to the privacy of the individuals and companies who participated in the study, but data can be shared in an anonymized form on reasonable request to the corresponding author.

References

Andersson L, Bryngelsson IL, Ohlson CG *et al*. (2009) Quartz and dust exposure in Swedish iron foundries. *J Occup Environ Hyg*; **6**: 9–18.

Baldwin PEJ, Yates T, Beattie H *et al*. (2019) Exposure to respirable crystalline silica in the GB Brick manufacturing and stone working industries. *Ann Work Expo Health*; **63**: 184–96.

Bello A, Mugford C, Murray A *et al*. (2019) Characterization of Occupational exposures to respirable silica and dust in demolition, crushing, and chipping activities. *Ann Work Expo Health*; **63**: 34–44.

BGIA. (2008) Institute for Occupational Safety and Health. Report 8/2006e. Exposure to quartz at the workplace. German Social Accident Assurance (GDUV). Available at https://www.dguv.de/ifa/publikationen/reports-download/bgia-reports-2005-bis-2006/bgia-report-8-2006/index-2.jsp Accessed 30 June 2021.

Boudigaard SH, Schlünssen V, Vestergaard JM *et al*. (2021) Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases: a nationwide cohort study. *Int J Epidemiol*; **50**: 1213–26. doi:10.1093/ije/dyaa287

Creely KS, Cowie H, Van Tongeren M *et al*. (2007) Trends in inhalation exposure—a review of the data in the published scientific literature. *Ann Occup Hyg*; **51**: 665–78.

Ge C, Peters S, Olsson A *et al*. (2020) Respirable crystalline silica exposure, smoking, and lung cancer subtype risks. A pooled analysis of case-control studies. *Am J Respir Crit Care Med*; **202**: 412–21.

Hammond DR, Shulman SA, Echt AS. (2016) Respirable crystalline silica exposures during asphalt pavement milling at eleven highway construction sites. *J Occup Environ Hyg*; **13**: 538–48.

Healy CB, Coggins MA, Van Tongeren M *et al*. (2014) Determinants of respirable crystalline silica exposure among stoneworkers involved in stone restoration work. *Ann Occup Hyg*; **58**: 6–18.

Hewett P, Ganser GH. (2007) A comparison of several methods for analyzing censored data. *Ann Occup Hyg*; **51**: 611–32.

HSE. (2014). *MDHS 101/2, Chrystalline silica in respirable airborne dust*. Health and Safety Executive.

Hughes JP. (1999) Mixed effects models with censored data with application to HIV RNA levels. *Biometrics*; **55**: 625–9.

IARC. (2012*)* IARC working group on the evaluation of carcinogenic risks to humans, WHO. Arsenic, metals, fibres, and dusts. In *Monographs on the evaluation of carcinogenic*

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

risks to humans. IARC Monograph No. Volume 100 C. Lyon, France: WHO. Available at https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Arsenic-Metals-Fibres-And-Dusts-2012 Accessed 30 June 2021.

ILO. (2004) *International Labor Organisation*. ISCO, International Standard Classification of Occupations. Available at https://www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm. Accessed 30 June 2021.

IOM. (2011) Institute of Occupational Medicine (IOM). SHEcan report: health, socio-economic and environmental aspects of possible amendments to the EU Directives on the protection of workers from the risks related to the exposure to carcinogens and mutagens at work. Respirable chrystalline silica. SHEcan P 937/8. Available at http://www.occupationalcancer.eu/projresults.html. Accessed 30 June 2021.

Miller FW, Alfredsson L, Costenbader KH *et al*. (2012) Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. *J Autoimmun*; **39**: 259–71.

Peters S, Vermeulen R, Portengen L *et al*. (2011) Modelling of occupational respirable crystalline silica exposure for quantitative exposure assessment in community-based case-control studies. *J Environ Monit*; **13**: 3262–8.

Radnoff D, Todor MS, Beach J. (2014) Occupational exposure to crystalline silica at Alberta work sites. *J Occup Environ Hyg*; **11**: 557–70.

Rappaport SM, Goldberg M, Susi P *et al*. (2003) Excessive exposure to silica in the US construction industry. *Ann Occup Hyg*; **47**: 111–22.

Roney N, Faroon O, Williams M *et al*. (2019) Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological profile for silica*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Available at https://www.atsdr.cdc.gov/toxprofiles/tp211.pdf.

StataCorp. (2019) *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC. Book Stata Statistical Software: Release 16.

t Mannetje A, Steenland K, Attfield M *et al*. (2002) Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med*; **59**: 723–28.

The European Parliament and Council of the European Union. (2006) Regulation (EC) No 1893/2006 of the European Parliament and of the Council of 20 December 2006 establishing the statistical classification of economic activities. NACE Revision 2 and amending Council Regulation (EEC). Available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32006R1893. Accessed 30 June 2021.

The European Parliament and Council of the European Union. (2017) DIRECTIVE (EU) 2017/2398 of the European Parliament and the Council of 12 December 2017 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017L2398&rid=1. Accessed 30 June 2021.

Tjoe Nij E, Höhr D, Borm P *et al*. (2004) Variability in quartz exposure in the construction industry: implications for assessing exposure-response relations. *J Occup Environ Hyg*; **1**: 191–8.

van Deurssen E, Pronk A, Spaan S *et al*. (2014) Quartz and respirable dust in the Dutch construction industry: a baseline exposure assessment as part of a multidimensional intervention approach. *Ann Occup Hyg*; **58**: 724–38.

Verpaele S, Jouret J. (2013) A comparison of the performance of samplers for respirable dust in workplaces and laboratory analysis for respirable quartz. *Ann Occup Hyg*; **57**: 54–62.

Yassin A, Yebesi F, Tingle R. (2005) Occupational exposure to crystalline silica dust in the United States, 1988–2003. *Environ Health Perspect*; **113**: 255–60.

Zilaout H, Houba R, Kromhout H. (2020) Temporal trends in respirable dust and respirable quartz concentrations within the European industrial minerals sector over a 15-year period (2002–2016). *Occup Environ Med*; **77**: 268–75.

Downloaded from https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxab116/6471261 by guest on 11 January 2022

Bilag 2 Måledagbog, oplysningsskema

Kontakt:
Læge Signe Hjuler, Arbejdsmedicin tlf. 6136 9465
Laborant Ole Dam, tlf. 9352 1013

Måle ID_______________________

(udfyldes af projektet)

Måledagbog - Registrering af arbejdsmiljø:

Tak for din deltagelse i støvmålingerne.
Vi har brug for nogle få oplysninger, mens og efter du har måler på.

Dato___________________

Navn____

Adresse____

E-mail____

Fødselsdag____

Fag____

Nummer på dit måleapparat _____________________________________

Måling starter kl. ____

Måling slutter kl.____

Pause (over 15 minutter), skriv tidsrum____________________________

☐ Jeg giver tilladelse til at billeder taget i forbindelse med mit arbejde må anvendes ved præsentation af projektets resultater.
Tilladelsen kan til enhver tid trækkes tilbage. ____

(Underskrift og dato)

Dagens vigtigste arbejdsopgave____

For opgaver over 1 time eller meget støvende:

Arbejdsopgave	Inde/ude	Værktøj el. redskab	Udsug på værktøj/maskine	Udsugning i rum	Åndedræts-værn	Støvreducerende arbejdsmetode	Hvis støvreducerende, angiv hvilken

Kontakt:
Læge Signe Hjuler, Arbejdsmedicin tlf. 6136 9465
Laborant Ole Dam, tlf. 9352 1013

Kontakt:
Læge Signe Hjuler, Arbejdsmedicin tlf. 6136 9465
Laborant Ole Dam, tlf. 9352 1013

Personal measurement form (project workdocument)

1. Date____________
2. Name of investigator_________________

Participant Detail:

3. First name:___________________
4. Last name:___________________
5. Project given ID:______________
6. Company name_______________
7. Industry:____________________
8. Profession:___________________
9. workplace:___________________
10. 1st worktask_________________
11. 2nd worktask_________________
12. 3rd worktask_________________
13. respiratory equipment_________

Measurement details:

14. Pump type__________________
15. Pump number_______________
16. Filter number_______________
17. Pump indicator, start_________
18. Pump indicator, end__________
19. Elapsed time, pump indicator: _________min

Flow rate

20. Flow rate at start_____________
21. Flow rate at end______________
22. Irregularities_________________

Blind filter

23. Blind filter number___________

Sampling time

24. Start time____________
25. End time_____________

26. Pause 1 start_________
27. Pause 1 end__________
28. Pause 2 start_________
29. Pause 2 end__________
30. Pause 3 start_________
31. Pause 3 end _________

Irregularities (e.g. termination of work due to..., an incident ect)

32. _________________________________
____

Bilag 3 Afslutningsskema til Arbejdsmiljøforskningsfonden