Occupational Exposure to Respirable Crystalline Silica, Styrene and risk of Autoimmune Rheumatic Diseases

PhD dissertation

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List of original papers including publication status

I. Determinants of quartz exposure levels across occupations in Denmark, 2018 [In preparation]

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III. A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases [Published at Occupational and Environmental Medicine]

Preface

This dissertation is a presentation and the conclusion of my PhD project *"Occupational exposure to respirable crystalline silica, styrene and risk of autoimmune rheumatic diseases"*. It was carried out at the Department of Occupational Medicine, Aarhus University Hospital, between 2016 and 2020, and funded by the Danish Working Environment Research Fund.

It has been a fantastic period, which has greatly expanded my knowledge on research in general, on epidemiology, biostatistics, exposure assessment and data management.

My main supervisor, Henrik Kolstad, has by all means contributed to this. By being inspiring, sharing his extensive knowledge in epidemiology, asking numerous questions and sometimes pushing me over the edge, when this was needed.

I also want to thank my other supervisors, Vivi Schlünssen, Hans Kromhout and Klaus Søndergaard for all their guidance and support, especially in the 11th hour. And as well to Hans for welcoming me in Utrecht.

Thanks to Kjell Torén, who has been an important part of the project group, always replying quickly with valuable comments. Statistician, Morten Frydenberg and data manager, Jesper Medom Vestergaard, have been of great importance, helping me out a number of times, and having patience with me - I'm really impressed.

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My family, especially my children Selma, Gorm and Ebbe, and my husband, Thor have much of the credit for this project being such a good experience. Thor, you are supportive more than one could ever ask for, also believing in me, helping me and even making me smile, when I'm down. And most importantly, helping me to remember what is really important in life.

Signe Hjuler Boudigaard,
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List of abbreviations

ACPA	Anti-citrullinated antibodies
ACR	American College of Rheumatology classification criteria
ANCA	Antineutrophil cytoplasmatic autoantibodies
IARC	International Agency for Research on Cancer
CC	Case-control study
CHCC	Chapel Hill Consensus Conference-criteria
CI	Confidence Interval
CPR	Unique person identification number
CS	Cohort study
CVR	unique company tax identification number
DISCED	Danish education classification
DISCO	Danish version of International Classification of Occupation
DOC*X	Danish Occupational Cohort*X
FTIR	Fourier Transform infrared spectrometry
GM	Geometric mean
GSD	Geometric Standard Deviation
ICD 8/ICD 10	International Classification of Diseases, 8th and 10th version
IRR	Incidence Rate Ratio
ISCO	International Classification of Occupation
JEM	Job Exposure Matrix
OSHA	Occupational and Safety Health Administration
LOD	Limit of Detection
MDHS	Methods for the Determination of Hazardous Substances
NACE	European Classification of Economic Activities
NIEHS	National Institute of Environmental Health Science
NIOHS	National Institute for Occupational Health and Safety
SYNJEM	Job Exposure Matrix, developed for the SYNERGI project
RA	Rheumatoid arthritis
RCS	Respirable crystalline silica

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Introduction

Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis, and Sjögren's syndrome are distinct autoimmune rheumatic diseases, but with considerable overlap in pathogenesis, signs and symptoms. Hence, a common approach in the exploration of the epidemiology behind these diseases is considered reasonable (1).

Epidemiologic literature suggests exposure to respirable crystalline silica and organic solvent as occupational risk factors for some of the autoimmune rheumatic diseases (1-3).

Crystalline silica is a ubiquitous part of our environment, and exposure happens in a number of occupations within construction, the metal industry, and in mining and quarrying (4). Crystalline silica takes several forms, of which quartz is the most common form (4). In this dissertation I will use the term quartz when this is the only measured type of crystalline silica, and whenever other forms of crystalline silica are included, I will use the term crystalline silica.

Styrene is an organic, aromatic solvent, used in the production of reinforced and other plastics (5).

The overall aim of this dissertation is to examine occupational exposure to respirable crystalline silica, styrene and risk of autoimmune rheumatic diseases.

Background

Autoimmune rheumatic diseases

Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome are autoimmune rheumatic diseases. These diseases are characterized by autoantibodies, produced by the immune system and targeting host cells or proteins, resulting in inflammation and destruction of tissue or organs (1, 6).

Systemic sclerosis is characterised by excessive fibrosis and vasculopathy, which results in skin thickening, ischemia and wounds and often involvement of kidneys, lungs, heart and the gastro-intestinal tract (7).

In rheumatoid arthritis, a continuous synovial inflammation leads to destruction of cartilage and joints, and sometimes extra articular symptoms like interstitial lung disease, pericarditis, pleuritis, vasculitis, secondary Sjögren's syndrome. Rheumatoid arthritis is often classified according to presence of rheumafactor antibodies (seropositive or -negative) or anti-citrullinated antibodies (ACPA) (8).

Systemic lupus erythematosus often presents with a characteristic rash, and mucous membranes and organs like lungs, kidneys and the brain are affected (9).

Small vessel vasculitis is defined by inflammation in the smallest vessel of the body, which leads to tissue and organ damage (10, 11). Small vessel vasculitis is a nomenclature for a group of diseases including antineutrophil cytoplasmatic autoantibodies(ANCA)-associated vasculitis and immune-complex vasculitis (11). Microscopic polyangiitis, granulomatosis with polyangiitis (Weegeners granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss) are all ANCA-associated vasculitis (10).

Primary Sjögren's syndrome is a disease with lymphocytic infiltration of lacrimal and salivary glands, with leads to glandular destruction. The syndrome is defined as secondary Sjögren's syndrome if another autoimmune rheumatic disease is present (12).

The prevalence of the autoimmune rheumatic diseases is low. The lifetime prevalence in Denmark is approximately 1 % (13) which corresponds well with other reported prevalence estimates (6, 14, 15). These diseases are chronic, associated with high morbidity and mortality, and incurable (2, 14), thus knowledge on risk factors is of great importance in terms of prevention.

The diagnostic procedure can be challenging and take time. The diagnostic criteria and disease classification has changed over time (14). The autoimmune rheumatic diseases affect primarily women, with a women:men ratio in a range from 9:1 in systemic lupus erythematosus to 3:1 in rheumatoid arthritis (8, 9, 13). Comorbidity between the diseases are considerable (13). The mechanisms behind the diseases are far from fully understood (1, 2, 6). Low concordance of the diseases of 20-30 % in twin studies, suggest that environmental risk factors play an important role in genetically predisposed individuals (6, 16, 17).

Occupational and environmental risk factors

Respirable crystalline silica and organic solvent are occupational exposures that have been associated with some of the autoimmune rheumatic diseases. Other occupational or environmental exposures that have been suggested include pesticides, asbestos, and infectious diseases (1, 3, 18-20). Smoking is a well-documented risk factor for rheumatoid arthritis and possibly also for systemic lupus erythematosus (2, 21-23).

Crystalline silica

Silica (SiO_2) has a crystalline or amorphous structure (24). Both have several polymorphisms. α- and β-quartz, cristobalit, tridymit are examples of crystalline silica among others, and changes in temperature result in transformation between the forms (25). Silica is a ubiquitous part of our environment, found in rocks, sands and soils. Most of the minerals in earth's crust contains silica, with quartz as the most common form (4, 26).

Workers employed in agriculture, construction, mining, quarrying, foundries, manufacturing of metals, ceramics, and glass are potentially exposed to respirable crystalline silica when sand, rocks, soils or products hereof are handled, produced, crushed, grinded or moved (24, 26). Route of exposure is primarily through inhalation of respirable particles (25). Exposure to respirable crystalline silica causes silicosis (27) and is classified as a group 1 human lung carcinogen by the International Agency for Research on Cancer (IARC) (4, 24).

Occupational exposure levels

Table 1 lists the more recent field studies on exposure levels of crystalline silica in different occupations and industries. Exposure to silica within high risk occupations has been documented for years (4). Generally, exposure levels have shown a decreasing trend over time (28-30), up to yearly decrease of 6 % across occupations and countries in Europe and Canada (30). Overall exposure concentrations in foundries have been reported in a range from geometric mean(GM) of 28 μg/m^3 in 2005 in Sweden to GM of 73 μg/m^3 in the USA (29, 31).

Measurements from The European Industrial Mineral Association (mines, quarries, plants) show an overall yearly downward trend of 3.9 % for respirable crystalline silica (28). Exposure concentrations within this industry in 2016 were generally low, with highest concentration seen among workers manufacturing clay products, being exposed at GM concentrations of 15 μg/m^3 and quarry workers as low as GM of 5 μg/m^3 (28).

Varying exposure concentrations to respirable quartz are still reported among construction workers. Measurements from 2009-2013 among Canadian brick layers and concrete workers revealed mean exposure concentrations (GM) of 105 μg/m^3 (32). In construction among concrete drillers mean exposure concentrations (GM) of 200 μg/m^3 are reported in the Netherlands in 2014 (33). But not all construction workers are high exposed, based on measurements from a number of European countries and Canada (SYNJEM database), bricklayers are estimated exposed at GM of 30 μg/m^3 and other construction workers at GM of 20 μg/m^3 (30).

Based on the SYNJEM database stone cutters and carvers are some of the highest exposed workers. Similarly, among Irish stone restoration workers using angle grinders to grind sandstone or granite respirable crystalline silica exposure levels (GM) of respectively 0.70 mg/m^3 and 0.06 mg/m^3 are reported (34).

Table 1. Summary of 12 recent exposure studies on exposure concentrations of respirable crystalline silica or quartz

Reference	Country Study period	Setting or study population	Samples	Exposure assessment	Results (geometric mean)	Remarks
Rappaport, 2003(35)	USA (1992-2000)	Survey data from 36 sites in 4 construction trades	151 samples	From surveys by i) centre to protect workers right, ii) NIOHS, iii) Mount Sinai School of Medicine RCS	Occupation, painters (when during abrasive blasting): 1480 µg/m^3 Occupation, bricklayers: 336 µg/m^3 Occupation, operating engineers: 52 µg/m^3 Occupation, labourers: 186 µg/m^3	Including repeated measurements
Nij, 2004(36)	The Netherlands, 1999	Construction workers		New samples, Respirable quartz	Occupation, overall 91 µg/m^3 Occupation, recess milling and concrete workers: 420 µg/m^3 Occupation, demolition workers: 140 µg/m^3 Occupation, inner wall constructors: 40 µg/m^3 Construction site cleaners: 20 µg/m^3	Including repeated measurements
Yassin, 2005(29)	USA 1988-2003	High risk industries, excl. mining and agriculture	7.209 Personal measurements	Database: Measurements of RCS collected at routinely inspections by US OSHA RCS	Overall: 77 µg/m^3 Industry, cut stone/stone products: 956 µg/m^3 Industry, grey iron foundries: 877 µg/m^3 Industry, stone work masonry: 732 µg/m^3 Overall downward trend (not specified)	Handling of values <LOD is unclear No repeats (repeats excluded)
Anderson, 2009(31)	Sweden, 2005-2006	11 Iron foundries	435 personal respirable quartz measurements	New measurements RCS	Overall: 0.028 mg/m^3 Occupation, shake out: 60 mg/m^3 Occupation, melters: 22 mg/m^3 Occupation, caster: 20 mg/m^3 Occupation, Transportation: 17 mg/m^3	No repeats

Table 1. Summary of 12 recent exposure studies on exposure concentrations of respirable crystalline silica or quartz

Reference	Country Study period	Setting or study population	Samples	Exposure assessment	Results (geometric mean)	Remarks
Peters, 2011(30)	Europe/Canada 1976-2009	All industries	23.640 personal quartz measurements	National exposure databases and exposure data from research institutes RCS	Occupation, stone cutters and carvers: 100 µg/m^3 Occupation, bricklayer (construction): 30 µg/m^3 Occupation, other construction worker: 20 µg/m^3 Occupation, farm worker: 20 µg/m^3 Overall downward trend of 6 %	Including repeated measurements
Healy, 2013(34)	Ireland Period:3 years, but not further specified	Stone workers doing maintenance of stone heritage buildings (on the site or at workshops	103 personal samples	New measurements, RCS	Task Grinding/cutting sandstone: 140 µg/m^3 Grinding/cutting granite: 30 µg/m^3 Grinding/cutting limestone: 5 µg/m^3	Including repeated measurements
Radnoff, 2014(32)	Alberta, Canada, 2009-2013	40 worksites in 13 industries across Alberta	343 personal samples	New measurements, Respirable Quartz	Occupations, bricklayer and concrete finisher: 105 µg/m^3 Occupation, labourers (non-mining: material handling, helpers, demolition) 32 µg/m^3 Occupations, truck drivers (incl. (un-)loading) 13 µg/m^3 Industry, demolition: 26 µg/m^3 Industry, foundry: 25 µg/m^3 Industry, sand and mineral processing: 90 µg/m^3	Including repeated measurements
Van Deurssen, 2014 (33)	The Netherlands, 2011-2012	Construction workers from 8 companies: Bricklayers Carpenters Concrete drillers Demolishers Tuck pointers	149 samples	New measurements, Respirable quartz	Occupations, overall: 100 µg/m^3 Occupations, concrete drillers: 200 µg/m^3 Occupations, tuck pointer: 180 µg/m^3 Occupations, demolisher: 120 µg/m^3 Occupations, bricklayers: 20 µg/m^3 Occupations, carpenter: 20 µg/m^3	Including repeated measurements

Table 1. Summary of 12 recent exposure studies on exposure concentrations of respirable crystalline silica or quartz

Reference	Country Study period	Setting or study population	Samples	Exposure assessment	Results (geometric mean)	Remarks
Hammond 2016(37)	Wisconsin, USA	Asphalt pavement site (11 construction sites: asphalt milling machine operators and ground workers)	42 personal measurements	New measurements RCS	Occupation, machine operator: 6 µg/m^3 / 4 µg/m^3 Occupation, ground worker: 6 µg/m^3 / 9 µg/m^3	Results stratified by manufacturer: hence 2 GMs No repeats
Bello, 2018(38)	Massachusetts, USA	Construction sites: Demolition, crushing and bridge repair sites	51 personal measurements, 33 air samples	New measurements RCS	Occupation, chipping workers: 527 µg/m^3 Occupation, crushing machine tenders: 93 µg/m^3 Occupation, labourer in demolition: 17 µg/m^3 Occupation, operating engineers: 6 µg/m^3	Some high exposed occupations: sampling of short duration to avoid overloading of filters. No repeats
Baldwin, 2018(39)	UK 1997-2013	Brick manufacturing and stone working sectors	699 measurements (269 new)	Measurements from 77 Occupational hygiene reports (1997-2013) New measurements (2013) RCS	Industry, brick sector: 77 µg/m^3 Industry, stone working sector: 171 µg/m^3 Occupation, hand mason (stone working industry): 450 µg/m^3 Yearly downward trend of 6 %, in stone working sector, not in brick sector.	Including repeated measurements
Zilaout, 2020(28)	Europe, 2002-2016	Mines, quarries and plants (163 sites, owned by 35 companies) located in 23 European countries	27.148 personal respirable quartz measurements	Industrial mineral association database of exposure (dust monitoring programme) RCS	Concentrations in 2016, RCS: Occupation, quarry worker: 5 µg/m^3 Occupation, miller operator 13 µg/m^3 Occupation, transport worker: 5 µg/m^3 Overall downward trend of 3,9%	Including repeated measurements

Abbreviation: RCS: respirable crystalline silica, OSHA: Occupational and Safety Health Administration, LOD: limits of detection, NIOHS: National Institute for Occupational Health and Safety

Risk factor for rheumatic autoimmune diseases

Respirable crystalline silica has been suggested as a risk factor for different autoimmune rheumatic diseases since the 1950'ies (40, 41).

Table 2 lists studies examining the association between respirable crystalline silica and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis. Only studies with specific diagnoses as outcome measurement are included, not studies with indirect outcome measurements nor mortality studies. Furthermore, only studies with silica exposure and not job titles are included.

Three studies examining the association between respirable crystalline silica and systemic sclerosis in men and in women (42-44) report a possible increased risk, but with considerable uncertainty in point estimates. One study finds no association in men, and no exposed cases among women (45). A Norwegian cohort study of male construction workers report an increased risk of 1.76 (95% CI 1.16-2.68), however this is the combined risk of systemic sclerosis, systemic lupus erythematosus and dermatomyositis (22).

Respirable crystalline silica increases the risk of rheumatoid arthritis in men (18, 21, 22, 46, 47). Two cohort studies use a quantitative exposure assessment; one shows no association (48), the other demonstrates an exposure-response association (47). The majority of the studies are able to distinguish between seropositive, seronegative or ACPA-positive, ACPA-negative cases. Two studies report an elevated risk of rheumatoid arthritis in both seropositive and seronegative cases (18, 22) while the others find that elevated risk is confined to seropositive or ACPA-positive rheumatoid arthritis (21, 46, 47). Only two studies of rheumatoid arthritis include women, one does not find an association (48), the other observes a weaker association compared to the results among men (18). Furthermore, in four of the studies smoking is an independent risk factor for rheumatoid arthritis, but also indicate an interaction between silica and smoking (18, 21, 22, 46).

The few studies on respirable crystalline silica and systemic lupus erythematosus give an indication of an association. However, the risk estimates of two of the studies are highly uncertain (49, 50), and one study does not stratify analysis by sex (51).
None of the studies on small vessel vasculitis are stratified by sex (52-56) and outcome measures among the studies are heterogeneous. The studies of primary systemic vasculitis (53) or ANCA associated small vessel vasculitis (54, 55) report increased risks of disease in silica exposed individuals. Stratified on subtypes of disease, respirable crystalline silica is associated with increased risks of Wegener's granulomatosis, and microscopic polyangiitis (52, 53, 55).

One study with quantitative exposure data (47), and five studies with semi-quantified exposure assessment (18, 44, 49, 50, 54) suggest that the association between silica and the autoimmune rheumatic diseases could be in a exposure-response dependent manner. However, exposure assessment in many of the studies rely on self-reported occupational history and specific exposures, and only few have included quantitative measurements for silica.
Generally, little is known in terms of quantitative exposure levels related to risk of disease, exposure-response relation or relevant time-windows of exposure (2, 3).

Table 2. Summary of 17 studies on the association between exposure to respirable crystalline silica and systemic sclerosis (n=4), rheumatoid arthritis (n=6), systemic lupus erythematosus (n=3) and small vessel vasculitis (n=4).

Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
Systemic sclerosis								
Diot, 2002 France (43)	CC (1998-2000)	F:69/138 [b] M:11/22 [b] Matched on age, sex, smoking	Self-report: occupational history and specific exposures Exposure assessment by blinded experts Exposure score =probability* intensity*frequency* duration	Medical records, ACR criteria	None	Ever-never: OR 13.04 (1.54-110.66)	Ever-never: OR 3.62 (0.64-20.40)	
Bovenzi, 2003 Italy (42)	CC (1997-1999)	F: 46/153 [b] M: 9/18 [b] Matched on age, sex	Self-report: occupational history and specific exposures. Exposure assessment by JEM Ever-never	Medical records, ACR criteria	Age	Ever-never: OR 2.4 (0.4-15.5)	Ever-never: OR 1.2 (0.1-15.8)	
Maître, 2004 France (45)	CC (1995-1999)	F:83/166 [b] M:10/40 [b] Matched on age, sex	Self-report: occupational history and specific exposures Exposure assessment by JEM Exposure score = intensity*frequency* duration	Register of systemic sclerosis ACR criteria	Education	No exposed cases	Ever-never: OR 0.9 (0.2-4.4)	Cumulative exposure score for men: indications of exposure response
Marie, 2014 France (44)	CC (2005-2008)	F:78/234 [b] M:22/66 [b] Matched on sex, smoking	Self-report: occupational history and specific exposures Exposure assessment by blinded experts. Exposure score =probability* intensity*frequency* duration	Medical records, ACR criteria	None	Ever-never: OR 3.08 (0.40-23.49)	Ever-never: OR 8.3 (2.58-29.60)	Cumulative exposure score in sex-combined analysis only: exposure response
Rheumatoid arthritis								
Turners 2000 (48)	Nested CC	F:15/60 [b] M:43/172 [b] Nested in cohort of workers in pottery and related industry. Matched on sex, age and date of 1st exposure.	Occupational history from medical examination records Exposure assessment in potteries by JEM, exposures in refractory- and sandstone industry by expert assessment Duration (y), mean conc. (μg/m^3), cumulative silica conc., (μg/m^3-y)	Diagnose (medical examination) registered at last surveillance scheme	Smoking, parity (women), coal mining employment (men)	Cumulative exposure (per 1000 μg/m^3-y): OR 1.13 (0.73-1.73)	Cumulative exposure (per 1000 μg/m^3-y): OR 0.71 (0.52-9.97)	No Exposure response
Stolt, 2010 Sweden (21)	CC (1996-2006)	M: 577/659 [b] Men only Swedish EIRA studies, matched on age, sex, residency	Self-report: occupational exposures (stone dust, rock drilling, stone crushing) Ever vs never (silica overall) High vs never (rock-drilling-never)	Medical records, ACR criteria RA, ACPA+ (anti-citrullinated peptide antibodies)	Age, residential area, social class		RA: Ever-never: OR 1.39 (0.98-1.96) High-never: OR 1.83 (0.97-3.43) RA, ACPA+: Ever-never:	Smoking: Strong independent risk factor Signs of interaction (smoking and silica)

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Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
							OR 1.67 (1.13-2.48) High-never: OR 2.34 (1.17-4.64)	
Yahya, 2013 Malaysia (46)	CC (2005-2009)	M: 149/213 [b] Men only Malaysian EIRA Matched on sex, age, residential area	Self-report: occupational exposures (stone dust, rock drilling, stone crushing) Ever vs never (silica overall) High vs never (rock-drilling-never)	Medical records, ACR criteria RA, ACPA+ (anti-citrullinated peptide antibodies)	Age, residential area		RA: Ever-never: OR 2.0 (0.9-4.6) High-never: OR 1.4 (0.4-4.9) RA, ACPA+: Ever-never: OR 2.4 (1.0-5.6) High-never: OR 1.5 (0.4-5.5)	Smoking strong risk factor: RA, ACPA+ non-silica and ever-never smoking: 2.7 (1.5-4.9) silica exposure and ever vs never smoking 7.5 (2.3-24.2)
Blanc, 2015 Sweden (22)	CS (1997-2010)	M: 241.077 713 RA cases Men only National cohort of construction workers, medical examination:2-5 years interval	Occupational title at first health examination Exposure assessment by JEM Ever vs never	National hospital register, ICD-10 codes RA, sero+/- Systemic sclerosis, lupus erythematosus, dermato-myositis combined (SSC, SLE, DM) (n=128)	Smoking, age		RA: OR 1.33 (1.11-1.60) RA, seropositive: OR 1.28 (1.02-1.61) RA, seronegative OR 1.46 (1.03-2.07) SSC, SLE, DM: OR 1.76 (1.16-2.68)	Smoking: independent risk factor. Smoking increases risk of RA, sero- in silica exposed
Vihlborg, 2017 Sweden (47)	CS (2001-2013)	M: 2187 silica 30 cases Men only Cohort of workers from 10 iron foundries	Company records: work history (1930-2005) Dust measurements (1968-2006) Exposure assessment by quantitative JEM Yearly mean silica conc. (mg/m3)	National hospital register, ICD-10 codes RA, sero+/-	None		RA SIR 1.52 (1.00-2.21) RA, sero+ Ever-never: SIR 1.70 (1.01-2.89) High-never: SIR 2.59 (1.24-4.76)	Exposure response relation
Ilar, 2019 Sweden (18)	CC (1996-2013)	F: 7622/77.902 [b] M: 3634/37.064[b] Matched on age, county, sex, index year.	Occupational titles from national census Exposure assessment by JEM Intensity (number of exposed occupation and year of exposure), ever-never	National health and medication registries, ICD 10	Sex, age, county, index year	RA: Ever-never: OR 1.2 (0.9-1.6) RA, sero + Ever-never: OR 1.4 (1.1-1.9)	RA: Ever-never: OR 1.6 (1.4-1.8) RA, sero + Ever-never: OR 1.7 (1.5-1.9)	Adjustment smoking, alcohol and asbestos resulted in slightly

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Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
						RA, sero – Ever-never: OR 0.8 (0.4-1.4)	RA, sero – Ever-never: OR 1.4 (1.2-1.6)	decrease in risk estimates. Semi-quantified: exposure-response
Systemic lupus erythematosus								
Parks, 2002 USA (49)	CC (1995-1999)	F: 240/321 [b] M: 25/34 [b] Carolina lupus study, matched on age, sex, state.	Self-report: occupational history and job tasks Exposure assessment by expert Intensity and certainty Never-low-high	Medical records, ACR criteria	Age, sex, state, race, education Stratified analyses: Sex, race, education, smoking	Medium-none OR 2.0 (1.0-4.0) High-none OR 3.3 (0.6-17.8)	Medium-none OR 3.0 (0.6-16.7) High-none OR 6.0 (0.7-48.0)	Semi-quantified: Exposure response Stratified on smokers: higher risk among ever smokers than non-smokers.
Finckh, 2006 USA (50)	CC (period not reported)	F=95/191[b] Women only Roxbury lupus project, matched on age and race.	Self-report: occupational history and job tasks. Exposure assessment by expert: Intensity and certainty Never-ever. Duration (1-5, >5 y)	Hospital database ACR criteria	Parity, smoking, educational level	Ever-never: OR 4.3 (1.7-11.2) Duration (1-5y) OR 4.0 (1.7-11.2) (>5y) OR 4.9 (1.1-21.9)		Semi-quantified: Exposure-response Smoking: not modify the effect.
Cooper, 2010 Canada (51)	CC (period not reported)	F:231/245[b] M: 27/18[b] Matched on age, sex, region	Self-report: occupational history and job tasks, incl. leisure activities with silica exposure Ever-never	Medical records ACR criteria	Age, sex, area	Men and women combined: Ever-never: Occupational exposure: OR 1.6 (0.9-2.7) Men: OR 3.0 (not shown) Women: OR 1.4 (not shown)		No association with smoking
Small vessel vasculitis								
Nuyts, 1995 Belgium (52)	CC (1991-1993)	F:3/6[b] M:13/26[b] Matched on age, sex and region	Self-report: occupational history Exposure assessment by blinded experts Ever-never	Medical records Wegener's Granulomatosis (WG) with renal involvement ACR[b] criteria (2 of 5)	None	Men and women combined: Ever-never: OR 5.0 (1.4-11.6)		

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Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
Hogan 2001 USA (55)	CC	65/176[b] F/M not reported Matched on sex, age and race	Self-report: occupational exposures & job tasks last 2 years Ever-never	Medical records ANCA associated small vessel vasculitis (SVV) incl. specific diagnoses	Smoking, pesticides, solvents, fuels, cleaning agents, glues, paints	<u>Men and women combined:</u> ANCA-Small vessel vasculitis: OR 4.43 (1.36-14.38) Wegener's granulomatosis: OR 3.5 (0.73-16.80) Microscopic polyangiitis: OR 5.0 (1.45-17.30)		
Lane, 2003 UK (53)	CC (1988-2000)	n=75/273[b] F/M not reported Matched on sex and age	Self-report: occupational history, Exposure assessment by JEM No-low-high High ever and high in index year.	National vasculitis register: ANCA associated primary systemic vasculitis. Incl. specific diagnoses CHCC or ACR criteria	Rural residence, social class, smoking	<u>Men and women combined:</u> High silica ever: Primary systemic vasculitis: OR 1.4 (0.7-2.7) High silica index year: Primary systemic vasculitis: OR 3.0 (1.0-8.4) Wegener's granulomatosis: OR 2.5 (0.8-8.5) Churg-Strauss syndrome: OR 5.6 (1.3-23.5) Microscopic polyangiitis: OR 3.2 (0.8-8.5)		No association with smoking
Hogan, 2007 USA (54)	CC (1997-2003)	F:52/58[b] M: 77/51[b] Matched on age, sex, and state	Self-report: occupational history (jobs>1 y), work tasks, and specific exposures Exposure assessment by experts: Silica score: duration*intensity*probability	Medical records ANCA associated small vessel vasculitis (SVV)	Age, sex, state	<u>Men and women combined:</u> Duration>21 year - never: OR 2.3 (1.0-5.3) High silica score - none OR 1.9 (1.0-3.5)		Semi-quantified (duration/exposure score): Exposure-response in analysis of duration

Abbreviations: CC: Case-control study, CS: Cohorts study, JEM: Job Exposure Matrix, F: Female, M: Male, ICD 10: 10th version of International Classification of Diseases, ACR criteria: American College of Rheumatology classification criteria, ANCA: Anti-neutrophil cytoplasmatic autoantibody, CHCC: Chapel Hill Consensus Conference

[a] Results: adjusted results shown, when analyses have included confounder adjustment.

[b] number of cases/controls

Styrene

Styrene is an organic, aromatic solvent produced by dehydrogenation of ethylbenzene. Styrene is used in the production of several plastic polymers and coatings (5, 57). High levels of styrene exposure are found in the work room air in the reinforced plastic industry. Especially during hand lamination of boats and wind mill rotor blades, and in the period before the 1990s (58).

Exposure to styrene is mainly associated with neurotoxic effects (59), and possibly non-malignant respiratory diseases (60) and lymphohaematopoietic malignancies (61). Styrene is classified as a group 2A human lung carcinogen by the International Agency for Research on Cancer (IARC) (57).

To our knowledge the association between autoimmune rheumatic diseases and styrene has not been examined, but associations with unspecified organic solvents, or aromatic solvents (i.e. styrene) have to a limited extent. Table 3 lists a summary of studies examining the associations between exposure to any organic solvent or aromatic solvent and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and primary Sjögren's Syndrome. As with table 2, mortality studies, or indirect outcome measurements are not included, as well as studies with job titles and no solvent-exposure assessment were not included.

Systemic sclerosis has been associated with exposure to any unspecified organic solvent (42-45, 62, 63), association with aromatic organic solvents is likely, but more uncertain (43, 44). Except for one study restricted to women (62), the possible association is seen in both men and women.

One study reports an association between any solvent and rheumatoid arthritis in women (20) but this is not supported in two other studies (64, 65). None of studies are stratified on ACPA- or sero-positive/negative status. One study on any solvents and systemic lupus erythematosus in women finds no association (19), while another study reports that solvent exposure with a duration of more than 5 year is potentially associated with increased risk of systemic lupus erythematosus in women (50).

Exposure to any solvents increases risk of any ANCA associated primary systemic vasculitis, and more specifically also Wegener's granulomatosis, but not microscopic polyangiitis (53). Increased risk of Sjögren's Syndrome is found following exposure to any solvent and specified to aromatic solvent (66). Neither of the studies on small vessel vasculitis nor Sjögren's syndrome report sex specific results.

Published literature on organic solvents, especially specified solvents, and autoimmune rheumatic diseases are limited. Except for one study (65), information of exposure in all the other studies relies on self-reported occupation, tasks or specific exposures reported at an interview in relation to study participation. Even though final exposure assessment includes a case-by-case expert review or assessment with a job exposure matrix, risk of recall bias remains. Furthermore, none of the studies include quantitative data. Few studies include a semi-quantified exposure assessment and reports on risk stratified at different exposure levels. Two of these shows increasing risk with increasing duration of exposure (50) or increasing exposure score(44), while two showed no signs of exposure response (19, 65).

Table 3. Summary of 13 studies on the association between exposure to solvents and systemic sclerosis (n=6), rheumatoid arthritis (n=3), systemic lupus erythematosus(n=2), small vessel vasculitis(n=1) and Sjögren's syndrome (n=1).

Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
Systemic sclerosis								
Nietert, 1998, USA(63)	CC (1995-1997)	F: 141/138 [b] M: 37/62[b] No matching	Self-report: occupational history and specific exposures Exposure assessment by JEM Exposure score =probability* intensity	Medical records, ACR criteria	Age at onset of disease	Cumulative intensity: Any solvent OR 1.1 (0.5-2.2) Max intensity: Any solvent OR 0.6 (0.2-1.9) Max probability: Any solvent OR 0.9 (0.5-4.2)	Cumulative intensity: Any solvent OR 2.9 (1.1-7.6) Max intensity: Any solvent OR 2.9 (1.2-7.1) Max probability: Any solvent OR 1.5 (0.6-4.0)	
Garabrant 2002 USA(62)	CC (1980-1992)	F:660/2227 [b] Women only Matched on age, race and residential area	Self-report: specific occupation, tasks and exposures Exposure assessment by blinded expert	Medical records, ACR criteria	Age and year of birth	Ever-never: Any solvent OR 2.0 (1.5-2.5)		
Diot, 2002 France (43)	CC (1998-2000)	F:69/138 [b] M:11/22[b] Matched on age, sex, smoking.	Self-report: occupational history and specific exposures. Exposure assessment by blinded experts. Exposure score =probability* intensity*frequency* duration	Medical records, ACR criteria	None	Ever-never: Any solvent OR 2.25 (1.01-5.05) Aromatic solvent OR 2.45 (0.80-7.70)	Ever-never: Any solvent OR 7.11 (1.40-36.12) Aromatic solvent OR 3.62 (0.64-20.41)	
Bovenzi, 2003 Italy(42)	CC (1997-1999)	F: 46/153 [b] M: 9/18[b] Matched on age, sex	Self-report: occupational history and specific exposures Exposure assessment by JEM Ever-never	Medical records, ACR criteria	Age	Ever-never: Any solvent OR 1.7 (0.6-4.6)	Ever-never: Any solvent OR 17.0 (1.3- >100)	
Maître, 2004 France (45)	CC (1995-1999)	F:83/166 [b] M:10/40[b] Matched on age, sex	Self-report: occupational history and specific exposures Exposure assessment by JEM Exposure score = intensity*frequency* duration	Register of systemic sclerosis ACR criteria	Education	Ever-never: Any solvent OR 2.8 (1.2-6.1) Aromatic hydrocarbons (benzene, toluene, xylene) OR 1.3 (0.4-3.8)	Ever-never: Any solvent OR 8.4 (0.9-78.6) Aromatic hydrocarbons (benzene, toluene, xylene) OR 1.4 (0.3-6.5)	Cumulative exposure score for any solvent, sex stratified shows no exposure response, but with very few (<2) cases and controls

Table 3. Summary of 13 studies on the association between exposure to solvents and systemic sclerosis (n=6), rheumatoid arthritis (n=3), systemic lupus erythematosus(n=2), small vessel vasculitis(n=1) and Sjögren's syndrome (n=1).

Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
Marie, 2014 France (44)	CC (2005-2008)	F:78/234 [b] M:22/66[b] Matched on sex, smoking	Self-report: occupational history and specific exposures Exposure assessment by blinded experts. Exposure score =probability* intensity*frequency* duration	Medical records, ACR criteria	None	Ever-never: Any solvent OR 1.86 (0.98-3.48) Aromatic solvent OR 26.4 (3.45- >100)	Ever-never: Any solvent OR 1.10 (0.37-3.24) Aromatic solvent OR 2.05 (0.60-19.22)	Cumulative exposure score in sex-combined analysis only: exposure response
Rheumatoid arthritis								
Lundberg, 1994 Sweden (65)	CS (1981-1983)	M: 375.035 F: 140.139 896 male and 629 female cases	Occupation stated in national censuses (1960+1970) Exposure assessment by JEM	National hospital register (ICD 8)	Age, residential area, urbanization	Limited use: Any solvent RR 1.0 (0.8-1.3) Substantial use: Any solvent RR 0.9 (0.3-2.8)	Limited use: Any solvent RR 1.1 (0.9-1.4) Substantial use: Any solvent RR 1.2 (1.0-1.6)	Semi-quantified: no sign of exposure response
De Roos, 2005, USA (64)	Nested CC	F: 135/675 [b] Women only Nested in cohort of 57000 licensed pesticide applicators and their spouses Matched on birthday	Self-report: occupational task at the farm	Self-reported diagnose, 23 % had physician validated diagnosis.	Age, state	Ever-never: Any solvents OR 0.6 (0.3-1.5)		
Parks, 2016 USA (20)	CS (1993-2010)	F: 24.018 275 cases Women only Cohort of 57000 licensed pesticide applicators and their spouses (farmers).	Self-report: occupational task at the farm	Self-reported diagnose, 79 % had physician validated diagnosis.	Age, state, pack-year of smoking	Ever-never: any solvents OR 1.6 (1.1-2.4)		Follow up on the cohort of De Roos, 2005 Association with smoking: increase in pack-years increases risk for RA
Systemic lupus erythematosus								
Cooper, 2004 USA (19)	CC (period not reported)	F:265/355 [b] Women only	Self-report: occupational history, job tasks, specific exposures Exposure assessment by expert: Intensity and probability	Medical records ACR criteria	Age, state, race, education	Moderate-none Any solvents OR 1.0 (0.57-1.9) Moderate/high-none Any solvents OR 1.0 (0.6-1.6)		Semi-quantified: no sign of exposure response

Table 3. Summary of 13 studies on the association between exposure to solvents and systemic sclerosis (n=6), rheumatoid arthritis (n=3), systemic lupus erythematosus(n=2), small vessel vasculitis(n=1) and Sjögren's syndrome (n=1).

Reference Country	Design, Period	Study population	Exposure assessment Exposure metrics	Outcome	Confounder adjustment	Results[a] Women	Results[a] Men	Remarks
Finckh, 2006 USA (50)	CC (period not reported)	F: 95/191 [b] Women only Roxbury lupus project, matched on age and race.	Self-report: occupational history and job tasks Exposure assessment by expert: Intensity and certainty Never-ever Duration (1-5, >5 y)	Hospital database ACR criteria	Parity, smoking, educational level	Duration (1-5y) <u>Any solvents</u> OR 1.04 (0.34-3.2) Duration (>5y) <u>Any solvents</u> OR= 2.1 (0.88-5.1)		Semi-quantified: indication of exposure-response Smoking: not modify the effect.
Small vessel vasculitis								
Lane, 2003 UK (53)	CC (1988-2000)	n=75/273 [b] F/M not reported Matched on sex and age	Self-report: occupational history Exposure assessment by JEM No-low-high High ever and high in index year	National vasculitis register: ANCA associated primary systemic vasculitis. Incl. specific diagnoses CHCC or ACR criteria	Rural residence, social class, smoking	<u>Men and women combined:</u> Ever-never: <u>Any solvents</u> Primære systemic vasculitis: OR 2.7 (1.1-6.6) Wegener's granulomatosis: OR 3.4 (1.3-8.9) Microscopic polyangiitis: OR 1.3 (0.1-12.9)		No association with smoking
Sjögren's syndrome								
Chaigne, 2015 France (66)	CC (2010-2013)	F: 159/318[b] M: 16/32[b] Matched on sex and age	Self-report: occupational history and specific exposures. Exposure assessment by expert and JEM: exposure score: probability * intensity * frequency * duration	Medical records (American-European consensus group criteria)	None	<u>Men and women combined:</u> Ever-never: <u>Any solvents</u> OR 2.76 (1.70-4.47) <u>Aromatic solvent</u> OR 3.03 (1.41-6.50) High cumulative-none <u>Any solvents</u> OR 2.25 (1.20-4.22) <u>Aromatic solvent</u> OR 2.50 (1.06-5.91)		

Abbreviations: CC: Case-control study, CS: Cohorts study, JEM: Job Exposure Matrix, F: Female, M: Male, ICD 8: 8th version of International Classification of Diseases, ACR criteria: American College of Rheumatology classification criteria, ANCA: Anti-neutrophil cytoplasmatic autoantibody, CHCC: Chapel Hill Consensus Conference

[a] Results: adjusted results shown, when analyses have included confounder adjustment.

[b] number of cases/controls

Disease mechanism

Central in development of autoimmunity, and later clinical disease, is the presence of autoantibodies directed at host cells, tissue and organs (1, 6).

One of the theories on development of autoimmune diseases is the occurrence of a number of triggering events, which in susceptible individuals will lead to serological autoimmunity first, and in some even clinical disease as well. Disturbed control mechanisms and loss of tolerance results in a continuous production of autoantibodies (1, 6).

Such triggering events could be exposure to respirable crystalline silica or styrene. The primary route of exposure is inhalation for both agents (25, 59).

The respired particles of crystalline silica are deposit in the alveoli of the lung, where macrophages phagocyte the particles. This results in secretion of cytokines, chemokines and lysosomal enzymes which further activates the antigen-presenting cells of the immune system and in turn the antibody producing cells (67, 68). Apoptosis of macrophages containing silica particles, results in release of the particles, new uptake by antigen-presenting cells, hence adding to the chronic inflammation (67).

In animal models it has been shown that styrene increases level of different cytokines; the interleukins IL-4, IL-5, IL-13 and IFNγ (69). These could play a role in the development of some, but not all of these diseases (70-72).

Hypothesis and aims of the thesis

Hypothesis

In this dissertation, the hypothesis is that occupational exposure to respirable crystalline silica or styrene, an organic solvent, is associated with an increased risk of systemic sclerosis, rheumatoid arthritis, lupus erythematosus and small vessel vasculitis in a dose-dependent manner.

Aims of the thesis

Study I

To quantify current exposure concentrations of respirable dust and quartz across a number of occupations in Denmark, and to examine determinants of quartz exposure.

Study II

To examine the association between occupational exposure to respirable crystalline silica and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis in the total Danish working population, 1979-2015.

Study III

To examine the association between occupational exposure to styrene and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome in a cohort of Danish styrene exposed workers, 1979-2012.

Materials and methods

Study overview

Table 4 summarizes the materials and methods in the three studies.

Table 4. Summary of material and methods

	Study I	**Study II**	**Study III**
Topic	Occupational exposure concentrations of respirable dust and quartz across occupations, and determinants	Association between occupational exposure to respirable crystalline silica and autoimmune rheumatic diseases	Association between occupational exposure to styrene and autoimmune rheumatic diseases
Design	Descriptive exposure study	Cohort study	Cohort study
Population	140 persons	3.012.274 general population workers 1.541.505 men 1.470.769 women	72.212 reinforced plastic workers 59.997 men 12.215 women
Follow up	2018	1979-2015	1979-2012
Exposure	Full shift work in 11 occupations	Respirable crystalline silica	Styrene
Exposure assessment	Diary	i. Employment history from the Danish Occupational Cohort (DOC*X) ii. SYNJEM (Nordic estimates): personal respirable silica measurements (1976-2009) and expert assessment	i. Employment history from the Danish Styrene cohort ii. JEM: personal styrene measurements (1970-2011), job task survey and information on company characteristics
Outcome	Respirable quartz	Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis	Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis, Sjögren's syndrome
Outcome assessment	Dust collected on 25 mm PVC filters using SKC LTD plastic cyclone. Determined gravimetrically and fraction of quartz determined with Fourier Transform infrared spectrometry (FTIR)	National Patient Register, ICD 8 and ICD 10 diagnoses	National Patient Register, ICD 8 and ICD 10 diagnoses
Confounders	None	Stratified by sex. Adjusted for age, decade, smoking probability, educational level	Stratified by sex Adjusted for age, decade, educational level
Main statistical analysis	Linear mixed effect model with worker, occupation and company as random effect, and tool and location as fixed effects	Logistic regression with person-years as unit of analysis	Logistic regression with person-years as unit of analysis

Study designs

Study I is a descriptive exposure study. Study II and III are both cohort studies, study II is a cohort of the general population and study III in an industrial cohort. In the following, the materials and methods for study I will be described, then study II and III will be described in parallel sections or together, when the method or materials used are the same.

Study I

Study population

The study population consisted of workers from 11 occupational groups based on the four-digit level of the Danish version of the International Classification of Occupations from 1988 (ISCO-88). The occupations were selected based on prevalence of potentially quartz exposed occupations in Denmark (24, 30, 73).

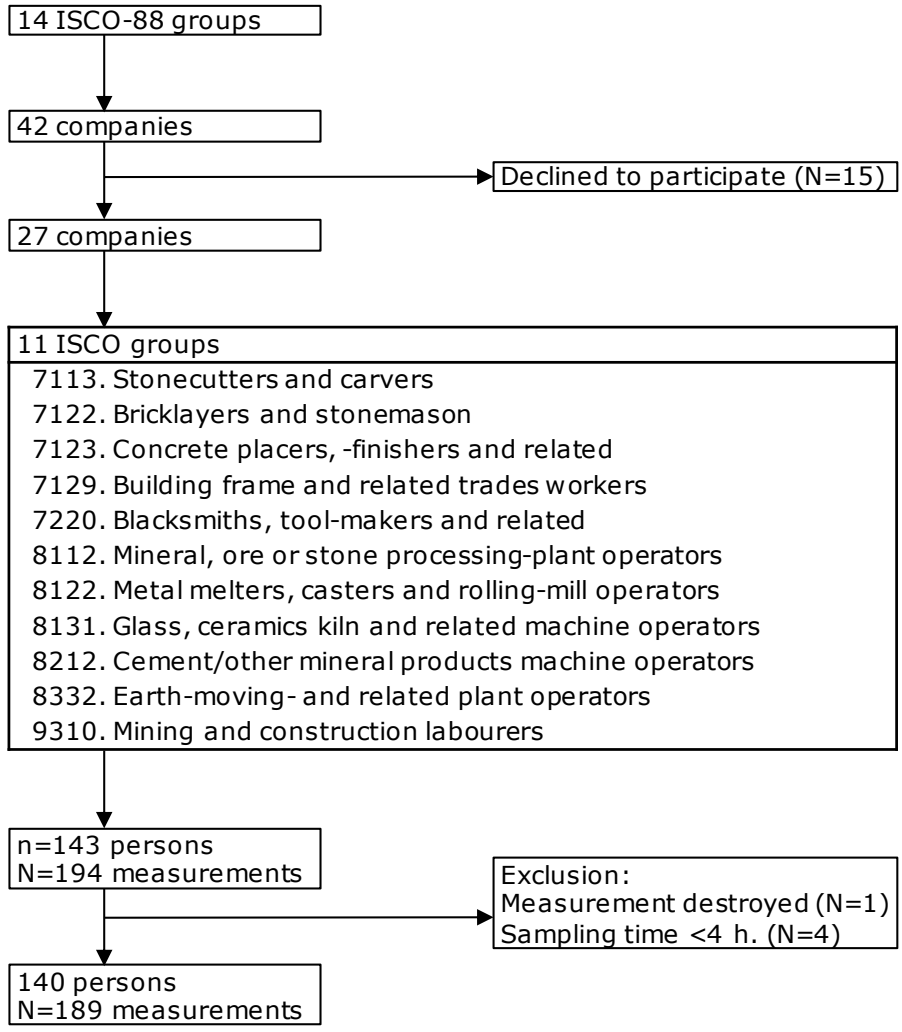


Figure 1. Flowchart of study I

After identification of 14 occupations, we contacted 42 companies, employing workers from these 14 occupations. 27 companies accepted the invitation. No farmers or electricians were successfully recruited, and low recruitment (<10 measurements) within some occupational groups resulted in the necessity of combining some groups on the corresponding 3-digit ISCO level (Figure 1).

Before the day of the measurement, the manager was instructed to select up to 8 participants, with a relevant occupation and performing tasks representative for the occupational group. All measurements were carried out by one skilled technician. All companies were asked to participate in a second survey, and we conducted repeated measurement on workers still employed at the worksite. In total, repeated measurements were carried out on 35 % of all participants.

In total 143 persons participated at least once, resulting in 194 measurements. We excluded measurements with short sampling time (below 4 hours) as well as one sample that lost content during transportation. The final study population consisted of 140 persons with 189 measurements (Figure 1).

Exposure assessment
During the day of measurement, the participants filled in a questionnaire on up to three work tasks, including the primary task, tools or construction machines used that day, use of respiratory equipment and if work was in- or outdoor.

Based on the primary work task, tools were categorized into: hand tools, power tools, operating construction machines or none and location was dichotomized into indoor or outdoor.

Sampling and analytical method
We collected the dust in a conductive plastic sampler with cyclone (SKC LTD plastic cyclone) on 25 mm PVC filters. We attached the sampler within the breathing zone, at the upper part of participant's chest and connected to an SKC AirChek XR5000 portable pump (SKC Inc., Eighty-Four, PA 15330, USA), calibrated at a flowrate of 2.2 l/min.

Respirable dust was determined gravimetrically. We used a Mettler UMT2 analytical scale (Mettler-Toledo Ltd, Greifensee, Switzerland) with a 0.1 mg precision. Before weighing, filters were conditioned for a minimum of 24 hours (22 °C, 45% relative humidity). We included one field blank per visit (n=45). The lower limit of detection (LOD) for respirable dust was calculated as: LOD_{RD} = 3*SD, with SD being the standard deviation of the weigh changes for the field blanks. LOD_{RD} was 25 µg.

Quartz dust was determined by Fourier Transform Infrared Spectrometry (FTIR), as recommended in the Health and Safety Executive instruction, MDHS 101/2 (74). The analytical LOD for quartz was 10 µg using this method.

Statistical analysis
Respirable dust and respirable quartz were lognormal distributed with the assumption that values below LOD follows the same distribution as the rest of the data. Hence all statistical analyses were performed on logarithmic transformed data. Due to the high number of left censored values, we used a mixed effects tobit model (metobit, STATA) for interval censored

data (75, 76). All the left censored values were assumed to be in an interval between (-∞) and value of LOD, and the model takes the distribution probability of censored data into account.

We included occupation, company and worker as random effects, and tool and location as fixed effects in a mixed linear effect model:

$$Ln(Y) = \beta_0 + \beta_{tool} + \beta_{location} + b_{1\text{-}11}occupation + b_{1\text{-}27}company + b_{1\text{-}140}Worker + \varepsilon,$$

with Ln(Y)=natural logarithm to quartz concentration,
β_0 = model intercept,
β_{tool} = categorical variable for tool,
$\beta_{location}$ =categorical variable for location,
$b_{1\text{-}11}$occupation = random effect term for occupation,
$b_{1\text{-}27}$company = random effect term for company,
$b_{1\text{-}140}$Worker= random effect term for worker,
ε = residual error term.

We calculated the geometric standard deviation factor as: $\exp\left(\sqrt{\sigma^2_{wY} + \sigma^2_{bY}}\right)$,

where σ^2_{wY} = within worker variance,
σ^2_{bY} = between worker variance.

Study II and III

In study II and III we used concordant materials and methods. Both studies were carried out in pre-existing cohorts; the Danish occupational cohort (DOC*X) of the total Danish working population (77) (study II) and the Danish Styrene Cohort, a cohort of workers employed at Danish companies producing reinforced plastic products (61, 78, 79) (study III). Next, registers, outcomes and main statistical methods for both studies are described, and subsequently final study population, exposure assessment and study specific analytical methods for study II and study III separately.

Registers

Table 5 summarizes the registers used for study II and III. Both cohorts obtain information on jobs and employment from Statistic Denmark: The Danish Styrene Cohort from the employment classification module and the Integrated Database for Labour Market Research, and DOC*X from the employment classification module, which is based on tax records, employers' mandatory reporting of occupation, self-reports to civil registration authorities and union membership (61, 77, 80). Jobs are coded according to the Danish version of the International Standard Classification of Occupations from 1988 (ISCO 88).

Table 5. Summary of registers

Register	Year	Information	Classification	Study II	Study III
Civil Registration System (81)	1968	- Unique person identification number (CPR) - Vital status - Sex - Place of residence	CPR[a]	x	x
Employment Classification module(80)	1976	By CPR: - Employment status - Occupation	CPR[a] DISCO[b]	x	x
Integrated Database for labour marked research(80)	1981	By CPR: - Occupation	CPR[a] DISCO[b]		x
National Central Business Register(82)	1999	Companies by unique tax identification number (CVR): - Calendar year - Production	CVR[c]		x
Supplementary Pension Funds Register(83)	1964-2007	By CPR workers' employment history: - industries - companies	CPR[a] NACE[d] CVR[c]		x
National Patient Register(84)	1977/1995	By CPR: - Diagnoses - from 1977: inpatients - from 1994: in- and outpatients	CPR[a] ICD-8[e] ICD-10[e]	x	x
Population's Education register(80)	1981	By CPR: -Highest attained education	CPR[a] DISCED[f]	(x)	x

[a] CPR = Unique person identification number
[b] DISCO 88 = the Danish version of International Standard Classification of Occupation
[c] CVR = unique company tax identification number
[d] NACE = European Classification of Economic Activities
[e] ICD 8/10 = International Classification of diseases, revision 8 and 10
[f] DISCED = Danish education classification

Through linkage to The Register of Danish Civil Registration System, the cohorts held information on sex, date of birth, vital status, place of residence and the unique personal identification number, which all Danish citizens have since 1968 (81). The unique personal

identification number allows for linkage with the National Patient Registry in order to identify cases (84). In 1977 The National Patient Registry was established with information on all diagnoses given at Danish public hospitals, from 1995 the register was updated with information from outpatient clinics. We included a two year "wash-out" period in order to reduce number of prevalent cases, hence follow up begins at the earliest in 1979 in both study II and study III.

Outcome

Outcome definitions in both studies are based on diagnose classification in the National Patient Registry (Table 6) (84). The type of diagnoses includes primary, secondary, referral, procedure and temporary diagnoses, we only included primary and secondary diagnoses of autoimmune rheumatic diseases. In the registry all contacts are codes with a diagnose-code, the 8th version (ICD-8: 1977-1993) and 10th version (ICD-10: 1994-2012) of the International Classification of Diseases.

Table 6. Summary of diagnose codes (ICD 8 and ICD 10) used in study II and study III.

Diagnose	ICD 8	ICD10	study II	study III
Systemic sclerosis		M34	x	
	73400	M340	x	x
	73401	M341	x	x
	73402	M342	x	x
	73408	M342A-B	x	x
	73491	M348	x	x
		M348B	x	x
		M349	x	x
Rheumatoid arthritis		M05	x	
	71219	M050	x	x
	71229	M051	x	x
	71238	M051A-F	x	x
	71239	M052	x	x
		M053	x	x
		M058	x	x
		M059	x	x
		M06	x	
		M060	x	x
		M068	x	x
		M069	x	x
Systemic lupus erythematosus		M32	x	
	73419	M320	x	x
		M321	x	x
		M328	x	x
		M329	x	x
Small vessel vasculitis	22709	M301	x	x
	44619	M310	x	x
	44629	M310A-B	x	x
	44649	M311	x	x
	44799	M311A	x	x
	44808	M313	x	x
	44809	M317	x	x
		M318	x	x
		M318A	x	x
		M319	x	x
Sjögren's syndrome	73490	M350		x

The two main differences are the inclusion of Sjögren's syndrome in study III, and that study II was conducted as 5 separate studies.

In study II we have five final study populations for further analysis. One for each disease of interest and one of any of the four diseases. Hence it was possible for a participant to experience one or more diseases. For instance, if a person was diagnosed with rheumatoid arthritis in 2002, he would then be censored from that year in the analysis of rheumatoid arthritis and the analysis of any of the diseases, while he would still contribute with person-years in the other three analyses until end of follow up due to a diagnose of one of these diseases, death, emigration, disappearance, or end of study.

In study III we had one final study population. Thus, a case was defined from the first year with a diagnose of any of the studied diseases, afterwards the person was censored and the possibility of having another diagnose was ignored.

In both studies, cases were defined according to the last given diagnose recorded within a calendar-year. This was to take into account the diagnostic procedure which can be time consuming, and sometimes several contacts are necessary before a final diagnose can be established (14).

Statistical methods

The associations between exposure to respirable crystalline silica or styrene, and the autoimmune rheumatic diseases were analysed in discrete time hazard models, using logistic regression models with person-years as unit of analysis (85). This yielded incidence rate ratios (IRR) presented with 95 % confidence intervals (CI). All analyses were stratified by sex, due to the high women:men ratio found in autoimmune rheumatic diseases (13).

For latency analyses, we analysed different metrics of respirable crystalline silica or styrene exposure accrued during several time windows in separate models. All exposure outside the specific time window was treated as zero. Exposure accrued within the window of interest was divided by the median resulting in a low and a high exposure group (86).

Study II

Final study population

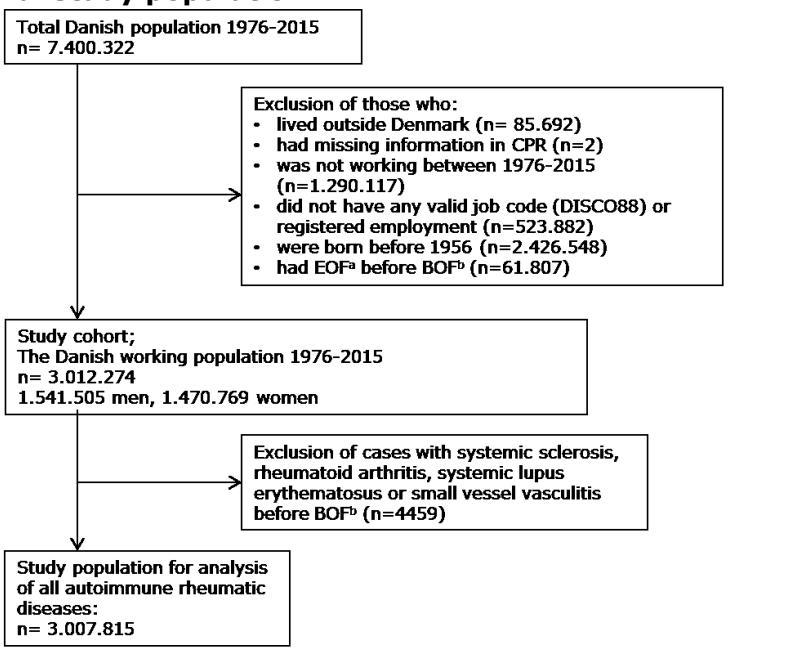


Figure 2. Flowchart of study II

From DOC*X and the CPR register, we identified all Danish residents from 1976-2015. We excluded those living outside Denmark, without valid registration in the CPR register, without any valid registered employment or job code (ISCO 88), and those who died, emigrated or disappeared before begin of follow up. Furthermore, we excluded all persons born before 1956, in order to have full employment history on all cohort members from at least 20 years of age. Resulting in a preliminary study population of all Danish residents, born from 1956 and onwards, with a minimum of one year of gainful employment and a valid job code, 1976-2015. The study population then included 3.012.274 persons; 1.541.505 men and 1.470.769 women (Figure 2).

Finally, in five separate procedures we excluded cases with either systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis, or all the mentioned autoimmune rheumatic diseases before begin of follow up resulting in five separate study populations for analyses (Figure 5).
Each person was followed from the year following his entrance on the labour marked but at the earliest in 1979. Follow up ends in case of disease, death, emigration, disappearance or end of study period (2015), whichever came first and the person was censored from that date.

Exposure assessment

The DOC*X cohort provides yearly information on job code and employment status. However, if ISCO code was missing in a year registered with active employment status, we assigned the latest valid ISCO code during the last five years, assuming that occupation is relatively stable.

Quantitative exposure level of respirable silica was based on the SYNJEM job exposure matrix (30, 87, 88). The SYNJEM was originally developed for the SYNERGI project, a pooled case control studies of lung cancer. The SYNJEM combines a JEM based on expert assessment (DOMJEM) with 23.640 personal measurements of respirable crystalline silica from European countries and Canada, modelling time and region specific respirable crystalline silica exposure estimates for all ISCO-68 job codes. For this study, we used only estimates for the Nordic countries in a modified version that provides estimates for ISCO-88 job codes. This modification was done by the researchers behind SYNJEM.

By combining information on annual job code and quantitative exposure level, all workers were assigned a yearly estimate of quantitative respirable silica exposure for each year of follow up.

Additional statistical methods
We used the following exposure metrics:

i. cumulative exposure (μg/m^3-year), the sum of exposure levels during all exposed years
ii. highest attained exposure intensity (μg/m^3), highest exposure level during all exposed years
iii. duration of exposure (years), sum of years with exposure>0
iv. mean exposure intensity (μg/m^3) cumulative exposure divided by the number of exposed years

Separately, for each exposure metric, we analysed the relation between respirable crystalline silica and autoimmune rheumatic diseases with grouped and continuous exposure variables. Study participants were grouped into exposed or non-exposed. Based on the tertiles of distribution of all exposed person-years for men and women combined, the exposed group was further divided into three equal-sized groups of exposure.

Time windows for latency analysis was divided into the previous 1-10 years, 11-20 years and >20 years.

We stratified all analyses on sex, and adjusted for age (≤25, 26-35, ≥36 years) and calendar year of follow up (1979-1984, 1985-1994, 1995-2004, 2005-2015). We did not have information on smoking or other life style factors on an individual level. In separate analyses, we additionally adjusted using a smoking JEM. The smoking JEM has been modelled from self-reported smoking habits reported in four large Danish population-based surveys for the DOC*X cohort. It provides sex and calendar year specific estimates for the probability of smoking for all ISCO 88 job codes (89). To account for other lifestyle factors, we adjusted for highest attained education level (primary, secondary or vocational, short cycle higher, medium cycle higher, long cycle higher education or unknown) in additional analyses, and we restricted analyses on cohort members working as blue-collar worker at baseline (ISCO codes 6000 to 9999).

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.

Study III

Final study population

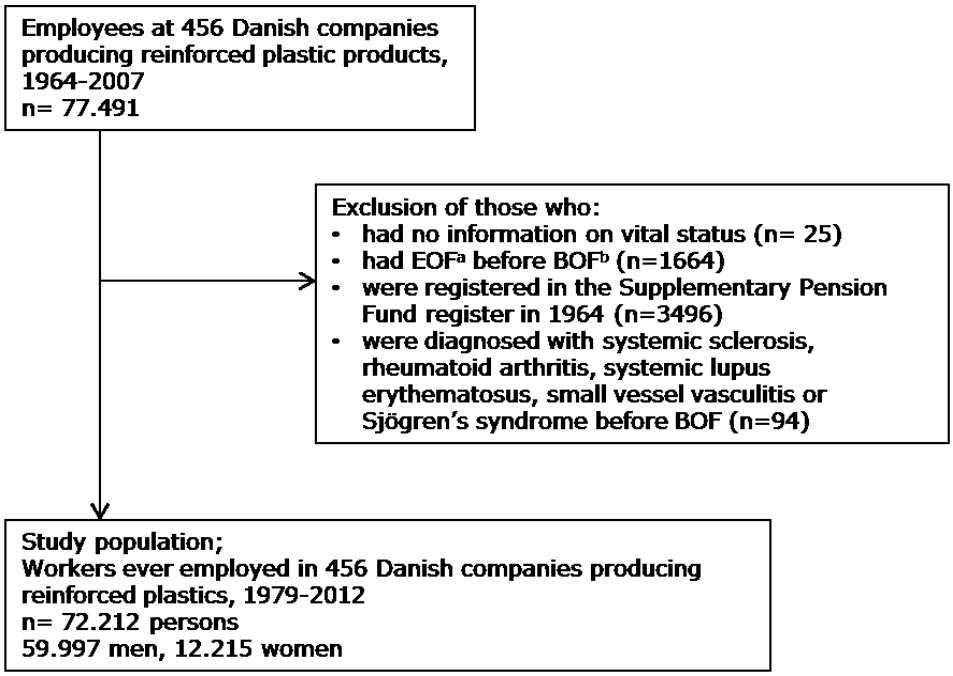


Figure 3. Flowchart of study III

The Danish Styrene Cohort was established in the 1990'ies and updated in 2012 (58, 61, 78). The 456 Danish companies, that produced reinforced plastic products since the early 1960s had been identified through their unique tax identification number at the National Central Business Register (82), and the 77.491 employees through the Supplementary Pension Fund Register (ATP) (83). This national register of mandatory pension saving for all Danish employees holds information of each person's employment history at companies and industries since 1964.

To obtain a complete work history, all persons with registration in 1964, the first year of the register, were excluded. Through linkage of the Danish Styrene cohort with the CPR register we excluded persons without information on vital status, those who died, disappeared, emigrated or were diagnosed with any of the studied autoimmune rheumatic disease before begin of follow up.

The study population then included 72.212 persons; 59.997 men and 12.215 women (Figure 3). The study population was followed from the first year of employment in one of the cohort companies, but at the earliest from 1979 until the year of disease, death, emigration, disappearance or end of study period (2012), whichever came first and after which the person was censored.

Exposure assessment
The Danish Styrene Cohort holds information on occupation for every year a worker is employed in one of the study companies. Occupation has been coded into four categories: white collar (ISCO-88 codes 1000 to 5999), skilled blue collar (codes 6000 to 7999), unskilled blue collar worker (codes 8000-9999) and others (e.g. student and retired workers) (61).

Within the Danish Styrene Cohort, an annual quantitative styrene exposure score was calculated for each cohort member. This styrene exposure score was calculated as the product of styrene exposure intensity and exposure probability. The exposure intensity was modelled from 1122 personal styrene measurements (1970-2011) and company information on main product, main process and calendar year. Based on a job task survey exposure probability was modelled giving odds of exposure for different worker characteristics (sex, occupation, calendar year) and company characteristics (main product and main process) (61).

Additional statistical methods
We used the following metrics to assess styrene exposure:
i. cumulated styrene exposure (mg/m^3-years), the sum of exposure scores for each year of employment in styrene production
ii. duration (years) of employment during styrene production
iii. mean styrene exposure intensity(mg/m^3), cumulative exposure level divided by the number of exposed years
iv. mean styrene exposure probability (%)

We analysed the relation between styrene and autoimmune rheumatic diseases with grouped and continuous exposure variables. We constructed three equal-sized groups of exposure based on the distribution of total person year for men and women combined.

Time windows for latency analysis was divided into the previous <5 years, 6-10 years, 11-15 years and ≥ 16 years.

We stratified on sex, and adjusted for age (≤39, 40-49, 50-59, 60-69, ≥70 years), calendar year of follow up (1979, 1980-89, 1990-99, 2000-09, 2010-12) and highest attained education level (secondary education, vocational education, short-, medium- or higher education).

All analyses were carried out using Stata v.13.

Summary of main results

Study I

In 189 measurements of respirable dust and respirable quartz, the median sampling time was 428 minutes (interquartile range 367-456 minutes). Six percent of the measurement of respirable dust and 38 % of respirable quartz resulted in levels below LOD.

Overall respirable dust was 220 µg/m^3 (2.64) High mean exposure concentration (GM(GSD)) to respirable dust was seen in occupation as metal melters and caster (730 µg/m^3 (1.96)), blacksmiths (720 µg/m^3 (2.50)) and other building frame workers (0.72 µg/m^3 (2.95)). The overall quartz exposure concentration was 20 µg/m^3 (2.64). The highest quartz concentration was found among stone cutters and carvers (GM 90 µg/m^3 (3.47)) and among metal melters and casters (GM 60 µg/m^3 (1.71)) (Figure 4).

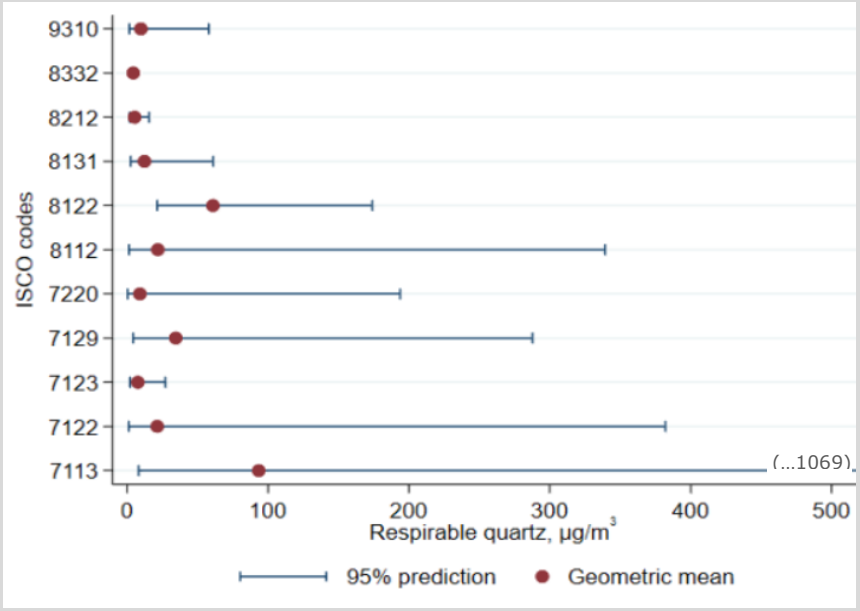


Figure 4. Geometric mean and 95 % prediction intervals of respirable quartz concentration in 11 occupations (ISCO 88) among 140 persons, Denmark, 2018.

Note:
ISCO 7113: The 95% PI continues to 1069 µg/m^3

Compared to not using any tools, the use of hand tool or power tool increased exposure concentration. Mainly power tool increased concentration with a factor 3.5. Between worker variance constitute 70 % of the total variance, and within worker to between worker variability ratio was 0.44. Including tools and location (fixed effects) only explained little of the total variance (13 %) (Table 7).

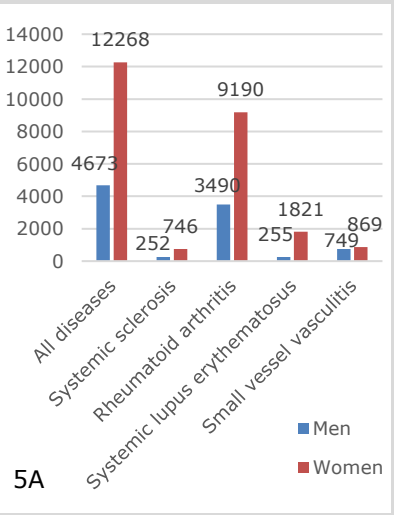
Table 7. Variance components for respirable quartz level from models excluding and including fixed effects

	Variance components in model excluding fixed effects (%)	Variance components in model including fixed effects (%)
Total between workers variance	1.37 (70)	1.09 (63)
Between occupations variance	0.53 (27)	0.45 (26)
Within occupations, between companies' variance	0.56 (29)	0.46 (27)
Within companies, between workers variance	0.28 (14)	0.18 (10)
Within worker variance	0.60 (30)	0.63 (37)
Total variance[1]	1.97 (100)	1.97 (100)
Sum of variance explained by random effects	1.97 (100)	1.72 (87)
Variance explained by fixed effects	-	0.25 (13)

Note: Table 7 is from the drafted manuscript: Determinants of quartz exposure levels across occupations in Denmark, 2018

Study II

Figure 5 summarizes the number of cases among the 1.541.505 male and 1.470.769 female workers and exposure distribution at end of follow up among the exposed workers, respectively 17 % of all male workers and 3 % of all female workers. Median cumulative exposure (interquartile range) was 60 µg/m^3-years (23-135 µg/m^3-years) for men and 33 µg/m^3-years (16 to 72 µg/m^3-years) for women.



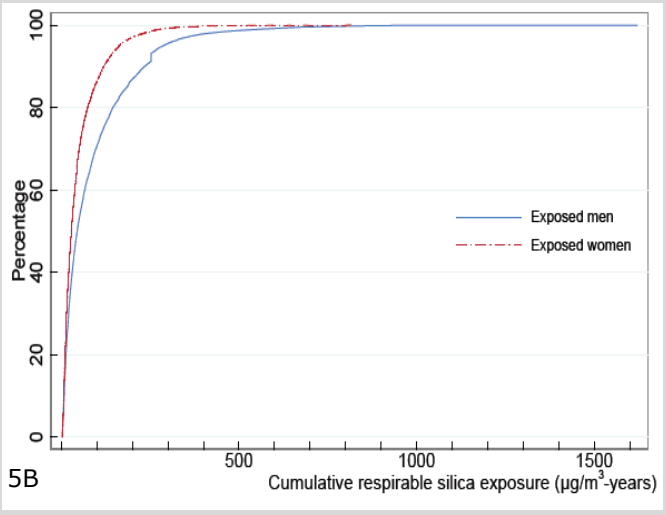


Figure 5A. Cases among 1.541.505 male and 1.470.769 female workers, 1979-2015. **Figure 5B**. Distribution of cumulative exposure at end of follow up among 266.325 men and 42.914 women

We observed an increased incidence rate ratio for predefined autoimmune rheumatic diseases combined of 1.53 (95% CI: 1.39-1.69) among men and 1.09 (0.87-1.37) among women when comparing the highest cumulative exposure strata with non-exposed, adjusted for age and calendar-year, (Figure 5 and 6). Furthermore, there is a tendency towards an exposure-response relation between exposure to respirable crystalline silica and risk of the autoimmune rheumatic diseases. The association was most evident in studies of rheumatoid arthritis and systemic sclerosis, and among men. Analyses of mean exposure intensity, highest attained exposure and duration of exposure yielded similar results (results not shown). Among men, mean exposure concentration between 2-10 µg/m^3 increased the risk of any of the studied diseases (IRR 1.42, 95% CI: 1.28-1.57). Risk of seropositive and seronegative rheumatoid arthritis was equally increased (results not shown).

In analyses of the association between systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis combined following cumulative exposure in restricted time windows of 1-10, 11-20 or more than 20 years ago, we saw a tendency towards a latency

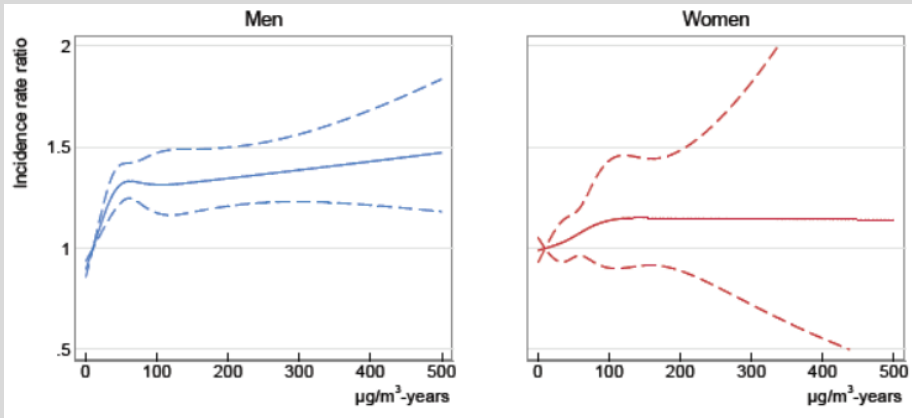


Figure 6. Restricted cubic spline fits of age and calendar year adjusted incidence rate ratios of autoimmune rheumatic diseases by cumulated respirable crystalline silica exposure in 1.541.505 men and 1.470.769 women, 1979-2015

effect of more than 20 years (Figure 7). Additional analyses adjusted for probability of smoking, highest attained educational level or restricted to blue collar workers among men only slightly decreased point estimates and did not change the overall patterns of an association (results not shown).

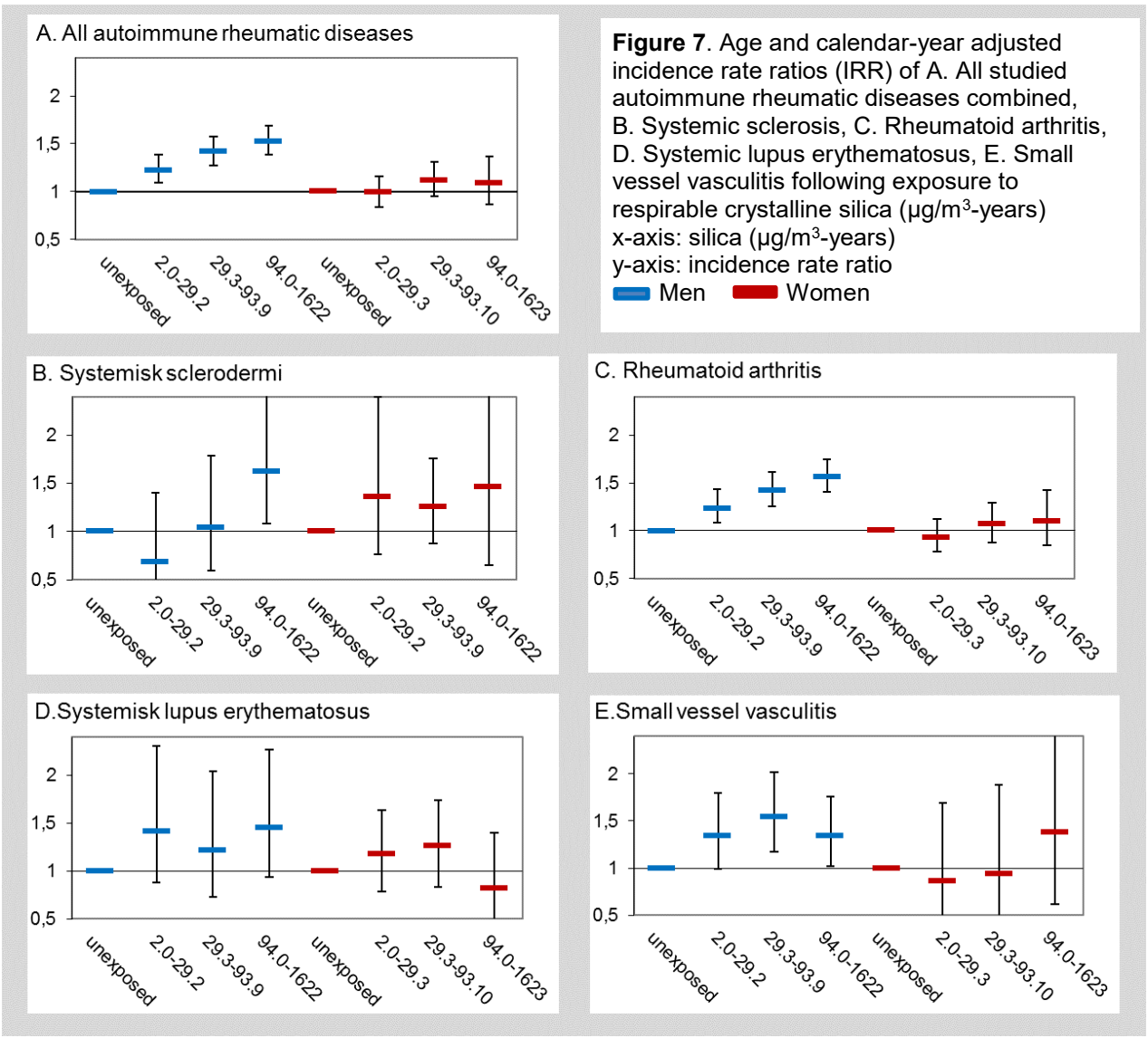


Figure 7. Age and calendar-year adjusted incidence rate ratios (IRR) of A. All studied autoimmune rheumatic diseases combined, B. Systemic sclerosis, C. Rheumatoid arthritis, D. Systemic lupus erythematosus, E. Small vessel vasculitis following exposure to respirable crystalline silica (µg/m^3-years)
x-axis: silica (µg/m^3-years)
y-axis: incidence rate ratio

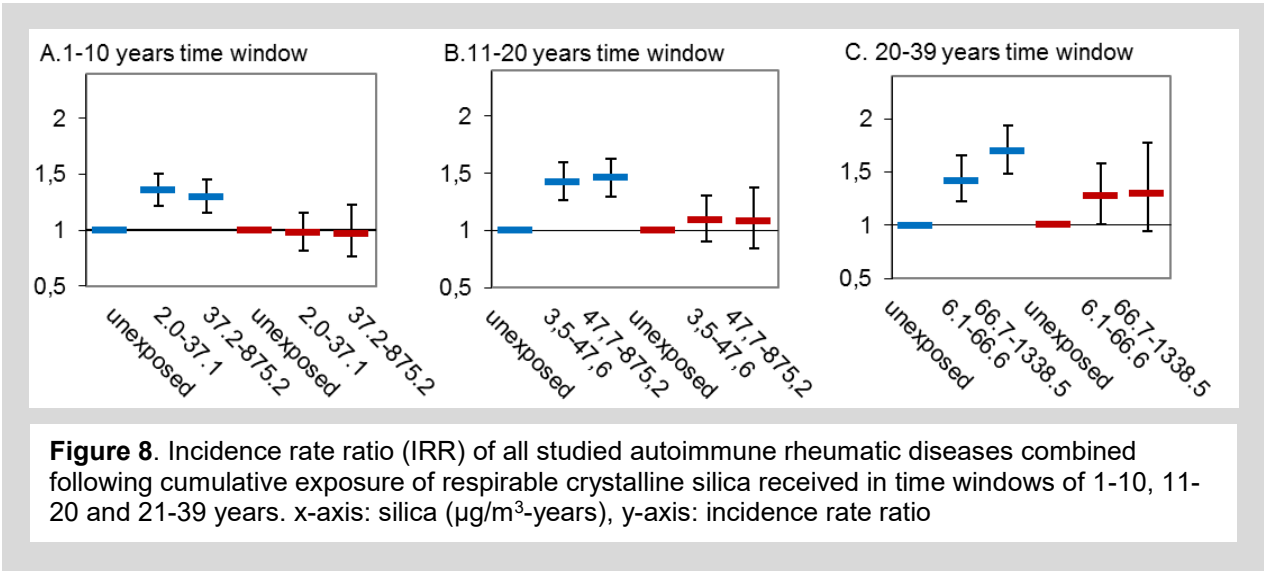


Figure 8. Incidence rate ratio (IRR) of all studied autoimmune rheumatic diseases combined following cumulative exposure of respirable crystalline silica received in time windows of 1-10, 11-20 and 21-39 years. x-axis: silica (µg/m^3-years), y-axis: incidence rate ratio

Study III

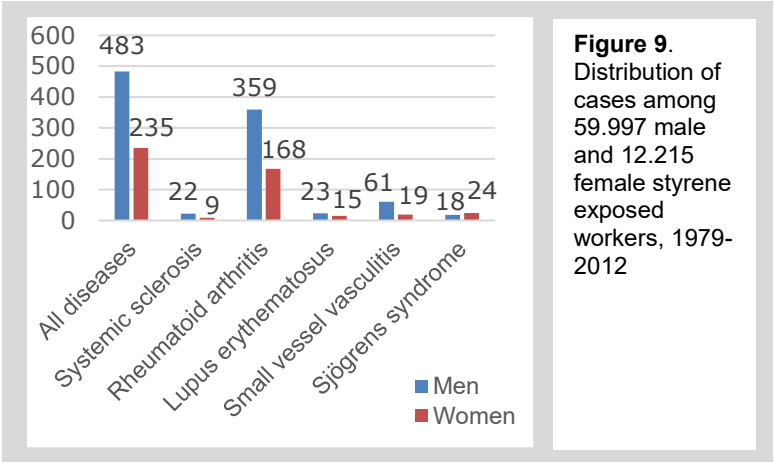


Figure 9. Distribution of cases among 59.997 male and 12.215 female styrene exposed workers, 1979-2012

Figure 9 summarizes the distribution of 718 cases identified during follow up.

In analysis adjusted for age, calendar year and highest attained educational level, we compared the strata of highest cumulative exposure with the lowest cumulative exposure, and observed an increased risk of systemic sclerosis among men of 1.86 (0.50-7.00) and among women of 2.50 (0.50-12.50), but with considerable statistical uncertainty (Figure 10). Furthermore, in men we observed an increased risk of rheumatoid arthritis, when comparing high with low cumulative exposure, but we did not see an increased risk of rheumatoid arthritis among women or systemic lupus erythematosus, small vessel vasculitis or Sjögren's syndrome in men nor women.

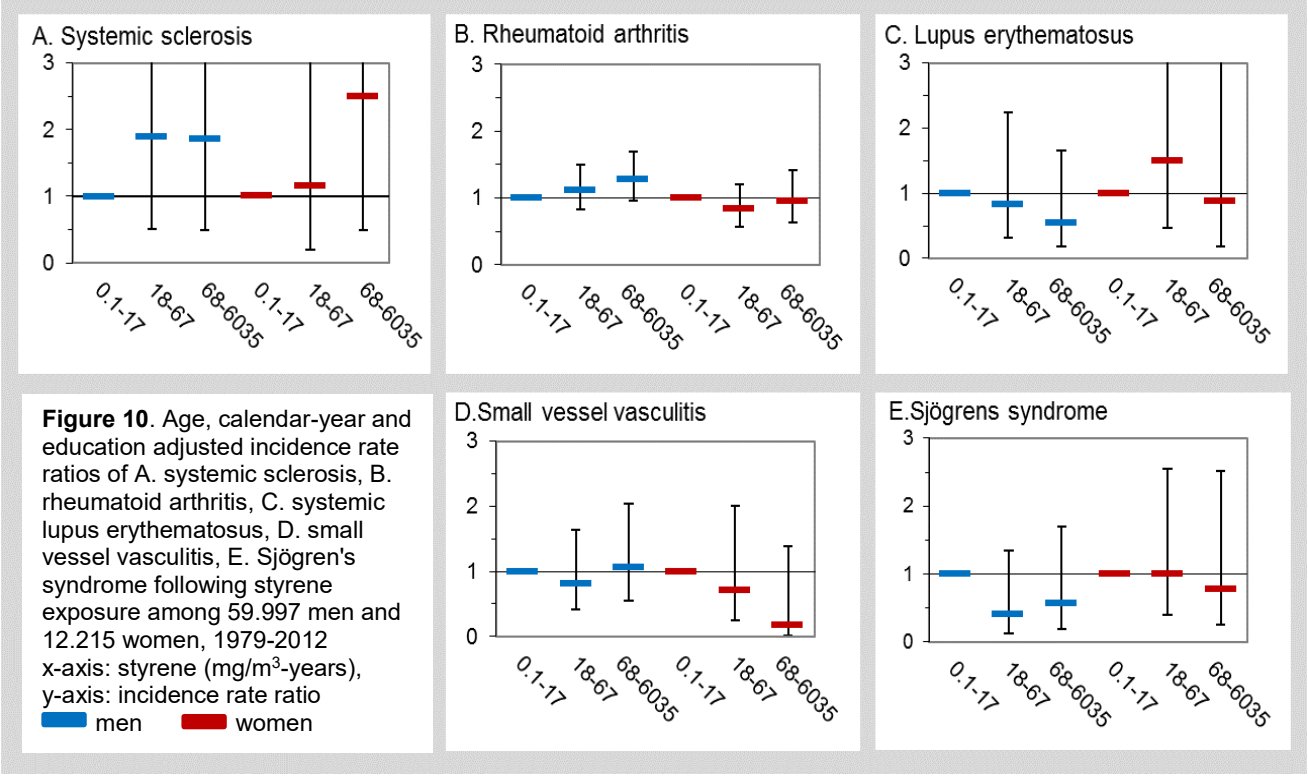


Figure 10. Age, calendar-year and education adjusted incidence rate ratios of A. systemic sclerosis, B. rheumatoid arthritis, C. systemic lupus erythematosus, D. small vessel vasculitis, E. Sjögren's syndrome following styrene exposure among 59.997 men and 12.215 women, 1979-2012
x-axis: styrene (mg/m^3-years), y-axis: incidence rate ratio
men women

In analysis of latency, we saw a tendency towards an increasing risk of systemic sclerosis following cumulative styrene exposure received more than 10 years prior in men (results not shown).

Discussion

Methodological considerations

Selection bias

In study I we recruited companies and workers to the field study. If companies with suspected low exposure levels were more prone to participate than companies with higher exposure levels it could underestimate mean exposure levels. At the worksite, the manager selected potential study participants. Here, workers, who had the dustiest work, could be more prone to participate, which could result in an overestimation of mean exposure levels. However, it is likely that these two biases are counteracting, but unknown to which extent.

In study III, the Danish Styrene cohort includes the majority of all Danish companies in the reinforced plastics industry and workers ever employed in these companies have been identified through national registers with high coverage. In study II, the whole Danish working population is included in the DOC*X cohort, also identified through the national registers. In Denmark all inhabitants have free access to general practitioners and hospital care. Limiting major selection bias.

Information bias

Misclassification of exposure

In study I, self-reported information on location, tool and primary task could be misclassified, however it is unlikely that workers have knowledge about the fraction of quartz in dust, hence potential misinformation would be related primarily to exposure, and result in non-differential misclassification. Any misclassification of workers into occupational group are presumably nondifferential, and the potential misclassifications would most like underestimate group mean.

In study II and III exposure information is based on national labour market registers and job exposure matrices (JEM), not influenced by recall bias. The JEMs provide group mean values, potentially causing non-differential misclassification of individual exposure level. However, the group mean should mainly be affected by Berkson type error, resulting in little or no attenuation in the effect estimates (90).

Estimated average exposure levels in JEMs have been suggested to capture the true exposure of women less correctly, partly due to gender differences in job tasks (91, 92). In study III, sex is included in the styrene JEM, generating sex specific group estimates. In the SYNJEM used in study II, sex is not included. This could potentially misclassify women to higher exposure levels. However, in the DOC*X cohort only 3 % of the women hold a silica exposed job, and this is probably more influential on the weaker association between respirable crystalline silica and autoimmune rheumatic diseases observed in women compared to men.

Misclassification of outcome

In study I we used the SKC LTD plastic cyclone at a flowrate of 2.2 l/min, which potentially have overestimated exposure levels of respirable quartz (93). This misclassification mainly has an effect on the estimation of group mean values, while analyses comparing exposure levels and determinants are less vulnerable to the exact values.

Furthermore 38 % of the measurements were below the analytical limit of detection (LOD). This could be caused by low exposure levels or short-time measurements. Since we excluded measurements lasting less than four hours, and median duration was 428 minutes (interquartile range:367-456 minutes), the values <LOD are likely to be caused by truly low exposure levels. The high proportion of values <LOD could result in overestimation of the mean particularly the geometric mean if treated improperly (94). In the statistical models all values <LOD were assumed to be in the range between (-∞) and the value of LOD. This method should reduce potential overestimation (75).

In study II and III, cases were identified by diagnose codes obtained from national health registers, not influenced by recall bias. Positive predictive values of 79 % for rheumatoid arthritis (95), 94 % for systemic sclerosis (96), and 73 % for systemic lupus erythematosus have been reported (97). Symptoms in autoimmune rheumatic diseases are overlapping, and it can be difficult to distinguish between diagnoses, hence the diagnostic procedures often require time, and initial diagnose might be temporary (14). If several diagnoses occurred within one year, we selected the last to enhance confidence in the diagnose. However, false positive cases could still result in non-differential misclassification and bias association towards the null.

Confounding

Gender is a is a strong risk factor for the autoimmune rheumatic diseases (13, 98) and in study II and III, women are less frequent and lower exposed to respirable crystalline silica or styrene. We chose to stratify all analysis by sex in study II and III, even though additional analyses did not suggest sex to cause effect modification. In both cohort studies, we adjusted for calendar time and age in analyses, to account for changes in diagnostic patterns over time and increased risk of disease with increasing age. Smoking, as well as other lifestyle factors related to socioeconomic factors, could have confounded risk estimates. In study III, we adjusted for highest attained educational level in order to capture some of the life style factors related to socio economic status. We did not have the possibility to adjust for smoking. A survey within the cohort showed decreasing smoking prevalence with increasing duration of employment (78), hence smoking is unlikely to have resulted in increased effect estimates. In study II, additional analysis with adjustment for education, for probability of smoking and analyses restricted to blue collar workers showed similar results with slightly decreased effect estimates.

In study II, we include the entire working population, hence exposure to environmental or occupational potential risk factors like solvents, pesticides, or asbestos could have confounded our results. Exposure to any of these are likely in silica- as well as non-silica exposed occupations, and would probably cause attenuation of risk estimates.

Power

Even with relatively large cohorts in study II and study III, a long follow up time and information retrieved from almost complete registers, the low number of cases still results in considerable uncertainty in our findings.

Key findings in light of other studies

Study I

The overall quartz exposure concentration(GM) of 20 µg/m^3 across occupations are low compared to current European Occupational Exposure limits (99), as well as low compared to overall exposure levels among U.S. workers (GM of 80 µg/m^3) based on measurements collected at work place inspections in all exposed industries (except farming and mining) by the Occupational and Safety Health Administration (OSHA), 1988-2003 (29). The differences in exposure levels could reflect actual lower exposure levels in Denmark, but it is likely that differences in measurement strategy (representative vs worst case in inspections) also contributes to the discrepancies.

Among construction workers, we found quartz exposure concentrations (GM) of 20 µg/m^3 among bricklayers and stonemasons, of 10 µg/m^3 among concrete workers and of 30 µg/m^3 among general building frame workers. This is in line with finding from SYNJEM, reporting mean exposure concentration (GM) of 30 µg/m^3 among bricklayers and of 20 µg/m^3 among other construction workers in Europe and Canada. However, these levels are lower than reported concentrations from other studies among construction workers (32, 33, 35, 36).

The highest exposed occupations in our study are stonecutters and -carvers with GM of 90 µg/m^3, similar to mean exposure concentration (GM) of 100 µg/m^3 reported in SYNJEM. Quartz exposure concentration among metal melters and casters are comparable with results from iron foundries in Sweden in 2005 (31).

We found that use of power tool increases exposure compared to no tools. This is in line with findings from studies within construction, which shows high concentrations at tasks with use of power tools (34, 39).

Study II

The increased risk of systemic sclerosis, rheumatoid arthritis, and possibly systemic lupus erythematosus and small vessel vasculitis with increasing exposure levels support the existing evidence linking exposure to respirable crystalline silica with autoimmune rheumatic diseases (2, 3, 67). We find a tendency towards an exposure-response. A Swedish cohort study of male foundry workers report exposure response relation between respirable crystalline silica and rheumatoid arthritis (47), however not supported in a cohort of pottery, sandstone and refractory material workers (48). A number of studies using semi-quantified exposure assessment (never, low, high score or increasing duration of exposure) have shown increasing risks with increasing exposure levels (18, 44, 49, 50, 54).

In many of the studies on respirable crystalline silica and autoimmune rheumatic diseases, association have either been assessed in men only (21, 22, 46, 47), or risk is higher among men than women (18, 20, 44, 51) We found that association between respirable crystalline silica and autoimmune rheumatic diseases was most evident among men, but showed similar patterns among women. The most likely reason is that few women in our cohort are exposed (3 %), and when exposed, at low cumulative exposure levels. The risk among men is found to be higher than the risk among women in two earlier meta-analysis on respirable crystalline silica and systemic sclerosis or rheumatoid arthritis (100, 101). However, sex-related differences in outcomes after exposure to crystalline silica was not supported in animal models of male and female lupus prone mice (102).

Recently, a number of studies have shown an association between smoking, exposure to respirable crystalline silica and increasing risk of seropositive or ACPA positive rheumatoid arthritis (18, 21, 22, 46). We did not have the possibility to stratify our analysis by smoking. In analysis adjusted for probability of smoking, the risk of rheumatoid arthritis and the other autoimmune rheumatic diseases remained increased.

In time-window analyses, we observed an increased risk of autoimmune rheumatic diseases with exposure received more than 20 years ago. This is in line with studies on systemic lupus erythematosus, where autoantibodies have been found years before development of clinical disease (103, 104) as well as studies on silicosis suggesting that much of disease progression happens after exposure to silica has ended (105).

Study III

We found indication of an association between exposure to styrene and systemic sclerosis, but not for the other autoimmune rheumatic diseases examined. The potential association to systemic sclerosis was suggested for both sexes, but based on very few cases. To our knowledge exposure to styrene has not previously been examined as a risk factor. Exposure to organic solvents more broadly has been suggested as a risk factor to systemic sclerosis. A meta-analysis from 2016 found an association between exposure to organic solvent and systemic sclerosis, with an increased meta-odds ratio of 2.72 (1.21-6.09) (106).

Few studies have reported an association between the use of solvents and rheumatoid arthritis (107), systemic lupus erythematosus (50), small vessel vasculitis (53) or Sjögren's syndrome (66). Our study showed inconsistent results for these diseases, but was based on few exposed cases.

An expert panel organized by the National Institute of Environmental Health Science (NIEHS) evaluated the evidence on environmental exposures and development of autoimmune diseases in 2014 and concluded that literature supported an association between organic solvents in general and risk of systemic sclerosis only, not the other autoimmune rheumatic diseases (2).

Conclusion and future perspective

Quartz exposure concentrations across a number of occupations in Denmark in 2018 are low compared to the European occupational exposure limit. Use of power tools increased quartz exposure concentration. The between worker variability between occupations and companies are considerable (Study I).

Our findings support that occupational exposure to respirable crystalline silica increases the risk of systemic sclerosis, rheumatoid arthritis and possibly also systemic lupus erythematosus and small vessel vasculitis in a dose dependent manner. Association was most evident among men, but few women were exposed (study II).

Based on few cases, we find indications that occupational exposure to styrene is associated with systemic sclerosis, but not rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis nor Sjögren's syndrome (study III).

We still have much to learn about the exposure patterns of respirable crystalline silica and development of autoimmune rheumatic diseases. The majority of the variability in exposure concentration in study I was between companies and occupations, indicating that a group based exposure characterisation (e.g job exposure matrix) is possible in studies on occupational exposure to respirable quartz (e.g. study II).

Our study II suggests that risk increases with exposure received more than 20 years prior, but more studies are needed to confirm this finding. In study I, we find that exposure levels of respirable quartz in Denmark is well below the European occupational exposure limit, however in study II, we observe an increased risk for several of the autoimmune diseases starting at very low mean exposure intensity levels. Hence, knowledge on threshold levels for development of autoimmune diseases is essential in terms of prevention.

Tools and location (fixed effects) explained 20 % of the total variability, hence prevention of dust exposure by e.g. dust reducing tools and procedures are still relevant.

Finally, our results on styrene and systemic sclerosis (study III) are suggestive, and need to be confirmed.

English summary

Background. Workers are exposed to dust from quartz and other crystalline silica when handling products of sand or stones. Styrene is an aromatic organic solvent used in the production of reinforced and other plastics. Respirable crystalline silica and organic solvents are suggested risk factors for autoimmune rheumatic diseases. We aimed to examine determinants of occupational levels of respirable quartz, and associations between occupational exposure to respirable crystalline silica or styrene and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis.

Methods. We conducted an exposure study (study I) among workers within 11 occupations including 189 full-shift personal measurements (35 % repeats) of respirable dust and assessed determinants of exposure levels across occupations. In two cohort studies of 3 million general population workers (study II) and 70.000 reinforced plastics workers (study III) established from national employment registers and followed since 1979, each worker was assigned an annual exposure level of crystalline silica or styrene based on quantitative job exposure matrices. We identified cases of autoimmune rheumatic diseases in a national patient register and examined sex specific incidence rate ratios (IRR) of autoimmune rheumatic diseases with 95% CI.

Results. Study I: We found an overall geometric mean, GM (geometric standard deviation) of respirable quartz exposure of 20 μg/m^3 (2.64). Stonecutters and carves were highest exposed (GM 90 μg/m^3 (3.47)). Use of power tools increase exposure concentration. Study II: Comparing high cumulative respirable crystalline silica exposure with no exposure, we observed an overall age and calendar year adjusted increased risk of autoimmune rheumatic diseases of 1.53 (1.41-1.75) in men and 1.09 (0.87-1.37) in women. The association was most evident for systemic sclerosis and rheumatoid arthritis. Study III: In adjusted analyses, and based on few cases, we observed an increased risk of systemic sclerosis in men (IRR=1.86; 0.5-7.0) and women (IRR=2.5; 0.5-12.5), when comparing the highest with the lowest cumulative styrene exposure tertiles.

Conclusion. Exposure levels across occupations in Denmark is low. Results support respirable crystalline silica as a risk factor for autoimmune rheumatic diseases, and styrene as a potential risk factor for systemic sclerosis.

Danish summary

Baggrund. Arbejdere udsættes for støv fra kvarts og andet krystallinsk silica, når produkter af sand og sten håndteres. Styren er et aromatisk, organisk opløsningsmiddel, der anvendes i produktionen af glasfiber og andet plast. Respirabelt, krystallinsk silica og organiske opløsningsmidler er mulige risiko faktorer for autoimmune bindevævssygdomme. Vi ønskede at undersøge determinanter i arbejdet for kvartsudsættelse, samt sammenhængen mellem erhvervsmæssig eksponering for respirabelt krystallinsk silica eller styren og systemisk sklerodermi, rheumatoid artritis, systemisk lupus erythematosus og småkarsvaskulitis.

Metode. Vi gennemførte et eksponeringsstudie blandt ansatte indenfor 11 jobgrupper, med 189 personlige målinger af respirabelt støv (35 % gentagne målinger) over en fuld arbejdsdag, og vurderede determinanter for eksponering på tværs af job (studie I). Vi udførte to kohortestudier, af hhv. 3 mio. arbejdstagere fra den almene befolkning (studie II) og 70.000 ansatte i glasfiber industrien. Begge kohorter er etableret ud fra nationale registre af arbejdsstyrken, følges fra 1979, og baseret på kvantitative job eksponeringsmatricer, tildeles alle arbejdere et årligt eksponeringsniveau af krystallinsk silica eller styren. Cases identificeredes i nationale patientregistre, og vi undersøgte kønsspecifikke incidensrate ratioer (IRR) for autoimmune bindevævssygdomme med 95 % sikkerhedsinterval.

Resultat. Studie I: Den overordnede geometriske gennemsnit, GM (geometriske standard deviationer) for kvartseksponeringskoncentration var 20 µg/m^3 (2.64). Stenhuggere var højest eksponeret (GM 90 µg/m^3 (3.47)). Anvendelse af elektrisk værktøj øgede koncentrationen. Studie II: Justeret for alder og kalenderår, og sammenligning af højt eksponerede med ikke eksponerede, så vi en øget risiko for de autoimmune bindevævslidelser samlet set på 1.53 (1.41-1.75) blandt mænd og 1.09 (0.87-1.37) blandt kvinder. Deen sammenhæng var tydeligst for systemisk sklerodermi og rheumatoid artritis. Studie III: Ved sammenligning af højeste og laveste eksponeringsstrata i justerede analyser, og baseret på få cases, så vi en øget risiko for systemisk sklerodermi blandt mænd (IRR=1.86; 0.5-7.0) og kvinder (IRR=2.5; 0.5-12.5).

Konklusion: Eksponeringsniveauer for kvarts på tværs af jobgrupper er lav i Danmark. Vores resultater støtter at respirabelt krystallinsk silica er en risiko faktor for autoimmune bindevævslidelse, og at styrene er en mulig risiko faktor for systemisk sklerodermi.

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Original manuscripts

Paper I.

Boudigaard, SH, Hansen, K, Kolstad, HA, Kromhout, H, Schlünssen, V. Determinants of quartz exposure levels across occupations in Denmark, 2018 [*In preparation*]

Paper II

Boudigaard, SH, Schlünssen, V, Vestergaard, JM, Søndergaard, K, Torén, K, Peters, S, Kromhout, H, Kolstad, HA. Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases, a nationwide cohort study [*Accepted, International Journal of Epidemiology, 2020*]

Paper III.

Boudigaard, SH, Stokholm, ZA, Vestergaard, JM, Mohr, MS, Søndergaard, K, Torén, K, Schlünssen, V, Kolstad, HA. A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases. *Occupational and Environmental Medicine. 2020; 77(2):64-69*

Paper I.

Boudigaard, SH, Hansen, K, Kolstad, HA, Kromhout, H, Schlünssen, V. Determinants of quartz exposure levels across occupations in Denmark, 2018 [*In preparation*]

Determinants of quartz exposure levels across occupations in Denmark, 2018

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Abstract
Background: High airborne concentrations of respirable quartz are reported from workers in construction, foundries and quarries. Current exposure concentrations in prevalent but presumably lower exposed jobs are less examined.

Aim: To quantify exposure concentrations of respirable dust and quartz across 11 occupations with expected high exposure concentrations in Denmark in 2018, and furthermore to identify determinants of respirable quartz exposure across several occupations.

Method: 189 full-shift personal samples of respirable dust within 11 occupations were sampled and analysed for quartz content with infrared spectrometry. Determinant for respirable quartz were analysed with mixed linear effect models.

Results: The overall geometric mean, GM (geometric standard deviation, GSD) for respirable dust and quartz was 220 µg/m^3 (2.64) and 20 µg/m^3 (2.64), respectively. Highest quartz concentrations were observed among stone cutters and carvers (90 µg/m^3 (3.47)), and metal melters and casters (60 µg/m^3 (1.71)). Use of power tools increased exposure concentrations with a factor 3.5. High variability in quartz exposure between occupations and between companies was observed.

Conclusion: This study shows that exposure concentration in 2018 in Denmark across a range of prevalent occupations with expected quartz exposure is well below the current occupational exposure limit. Use of power tools increases exposure concentration. Most of the variability in exposure concentration was seen between occupations and between companies.

Background

Crystalline silica is present in most rocks and is the major constituent of sand and soil globally. Alpha-quartz is the most abundant of several forms of crystalline silica (1, 2). 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) (2, 3).

Workers in agriculture, construction, mining, quarrying and manufacturing of metal products may be exposed to high concentrations of respirable silica (2, 4). Respirable crystalline silica exposure is a well-documented risk factor for silicosis (5) and lung cancer (2, 6) and is associated with the occurrence of rheumatoid arthritis, systemic sclerosis and other autoimmune rheumatic diseases (7, 8).

In general, exposure levels of respirable crystalline silica have declined over the past 50 years (4, 9-11), but high levels are still reported in foundries (12, 13), the stone and brick sector (12, 14, 15), and in construction (12, 16) in certain countries. It has been estimated that 5.3 million workers in Europe were potentially occupational exposed to respirable crystalline silica in 2006; of which 75 % were employed in construction (17). However, not all construction workers are exposed at high levels (18). In order to implement an efficient preventive strategy, knowledge on exposure levels in prevalent but less exposed jobs are warranted in addition to the high exposed jobs.

The aim of the present study is to quantify current exposure concentration of respirable quartz in Denmark and to identify determinants of exposure levels across occupations.

Materials and methods

Companies and participants

Based on the prevalence of occupations, that according to the literature had a high probability of quartz exposure companies employing construction-, metal- and concrete workers and farmers were selected for participation (2, 4, 19). Occupations were selected based on the four-digit level of the Danish version of the International Standard Classification of Occupations (ISCO 88)(20) (Table 1). Industry was classified at two-digit level of the European classification of industries (NACE vers.2) (21). Companies located in the eastern part of Jutland and preferable with employees from more than one relevant occupation were prioritised. Managers were instructed to select up to eight employees with work tasks representative for the targeted occupation.

Sampling and analytical method

At the measurement day, participants filled in a questionnaire about primary task, tool or construction machine used, whether work was in- or outdoor, and use of respirator during that day. We conducted full-shift measurements, and pumps were turned off during breaks lasting more than 15 minutes. Measurements with sampling time below 4 hours were excluded. All companies were asked to participate in a second survey. If they agreed, repeated measurements were carried out on study participant who had remained at the worksite. All measurements were carried out by the same technician between April and December 2018.

Respirable dust were collected on 25 mm PVC filters using a conductive plastic sampler with respirable dust cyclone (SKC LTD conductive plastic cyclone) connected to SKC AirChek XR5000 portable pump (SKC Inc., Eighty-Four, PA 15330, USA) calibrated at a flowrate 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 hours (22 °C, 45% relative humidity) before weighing, which was performed using a Mettler UMT2 analytical scale (Mettler-Toledo Ltd, Greifensee, Switzerland) with a 0.1 mg precision.

One field blank was included per visit (n=45). The lower limit of detection (LOD) for respirable dust was estimated to 25 µg, assessed as 3 times the Standard deviation (SD) of the weight changes of the field blanks.

The content of quartz on the filters was determined by Fourier Transform infrared spectrometry(FTIR), in accordance with the Health and Safety Executive instruction, MDHS 101/2 (22). The analytical level of quantification for quartz using this method was 10 µg.

Statistical Analysis
Respirable dust and respirable quartz concentrations were lognormal distributed, when we assumed values<LOD followed the same distribution. Hence all statistical analyses were performed using log-transformed values. We used mixed effects tobit model (metobit, Stata) for interval censored data, all left censored values were assumed to be in an interval between (-∞) and the value of LOD (23, 24).

In a mixed effect model, worker, company and occupation were included as random effects, and tool and location as fixed effects. β-coefficients are shown with 95 % confidence intervals (CI). Geometric standard deviation factor (GSD) was calculated as $\exp\left(\sqrt{\sigma_{\mathrm{wY}}^2+\sigma_{\mathrm{bY}}^2}\right)$, where σ_{wY}^2=within worker variance and σ_{bY}^2=between worker variance.

If an occupation was represented by less than 10 measurements, it was merged with the other occupations on the ISCO major group 3 level. Tool was categorised into none, hand tools, power tools, and operating construction machines. (Table 1).

All analyses were carried out using Stata, version 16

Results
A total of 42 companies were contacted and 27 agreed to participate. We tried to contact farmers through a farmers' trade associations, but no farms were recruited.

We performed 194 measurements on 143 participants. One measurement was lost during transportation and four measurements with a sampling time less than four hours did not fulfil our inclusion criteria and were excluded, leaving 189 measurements from 140 participants in the analyses. The median sampling time was 428 minutes, with an interquartile range of 367-456 minutes. Repeated measurements were available for 35% of all participants. All together 15 % of workers reported use of respirators at some point during the day.

Six percent of the respirable dust measurements and 38 % of the quartz measurements were below LOD (Table 2). The overall respirable dust concentration was 220 µg/m^3 (2.64)). Highest exposure levels were found among metal melters and casters with GM (GSD) of 730 µg/m^3 (1.96), among blacksmiths (720 µg/m^3 (2.50)) and other building frame workers (720 µg/m^3 (2.95)) (Table 2).

The overall quartz exposure concentration was 20 µg/m^3 (2.64)). Highest exposure levels were observed among stonecutters and carvers (90 µg/m^3 (3.47)) and metal melters and casters (60 µg/m^3 (1.71).

Table 3 shows the β coefficient for respirable quartz concentrations. Use of hand tools or power tools compared to not using any tools were determinants for increased quartz exposure concentrations. The use of power tools resulted in a 3.5 times higher exposures compared to not using any tools (exp(β)=3.51 (1.66-7.41).

Variability in quartz exposure levels was mainly ascribed to differences between occupations (27% of the total variability) and between companies (29% of the total variability). The within to between worker ratio variability ratio was 0.44. Fixed effects (tool and indoor/outdoor)

explained 13 % of the total variability, and 20 % of the total between worker variability (table 4). The latter calculated as: $\frac{(\text{total variability(random effects model)}-\sigma^2_{WY}) - (\text{total variatility(fixed effects model)}-\sigma^2_{WY})}{(\text{total variatility(random effects model)}-\sigma^2_{WY})}$

Discussion

Based on 189 respirable dust measurements among 140 workers across 11 occupations in Denmark during 2018, the overall geometric mean exposure concentration was 220 µg/m^3 for respirable dust and 20 µg/m^3 for respirable quartz. The quartz exposure levels were low compared to the European and Danish occupational exposure limit of 100 µg/m^3 (25), and 38% of all measurements were below the analytical LOD. Use of power tools increased quartz exposure concentrations with a factor 3.5. Most of the variability in exposure concentration was seen between occupations and between companies.

Our results on quartz exposure concentrations among metal melters and casters are in line with results from iron foundries in Sweden in 2005 reporting overall exposure levels (GM) of respirable quartz of 280 µg/m^3, with two-fold increased level during shaking out and furnace and ladle repair (13).

Compared to earlier studies of construction workers (4, 12, 15, 16, 26-28), we find equal or lower concentrations. Measurements from 2009-2013 in Canadian construction workers showed a GM of respirable quartz of 105 µg/m^3 among bricklayer and concrete finisher(12). In our study the group of bricklayers and stonemasons are exposed to quartz at levels that are somewhat lower (GM of 20 µg/m^3). In the large pooled SYNJEM study, substantially higher levels of crystalline silica was found in Canada compared to Northern Europe (4). Our study shows comparable exposure levels as reported in SYNJEM for high exposed occupations (stonecutters and carvers, GM of 10 µg/m^3) and occupations with a high probability of exposure (bricklayers, GM of 30 µg/m^3) (4).

In our study, use of power tools increased quartz concentrations corresponding well with findings of other studies among construction workers (14, 15). However, the sample size limits number of occupations and numbers of measurements within each occupation included, and we did not have sufficient power to differentiate exposure concentration for tasks within occupations.

If workers of participating companies were less exposed than workers of those declining to participate, true exposure levels would be underestimated. Any misclassification of workers into occupational groups (ISCO88) are most likely non-differential and would probably underestimate group means. Self-reported information on in vs. outdoor location, tool and primary task could be misclassified, but since the workers are unaware of the level of respirable quartz this should also be non-differential.

The use of SKC LTD plastic cyclone has potentially resulted in oversampling of respirable quartz (29) and hence overestimation of exposure levels. In the mixed effect model the potential oversampling should have less effect on determinants of exposure and variance. Approximately 1/3 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 (30). Due to high numbers of values <LOD in our study, we refrained from imputation of the left censored values, and instead used a tobit model, that only takes the distribution probability of the missing values into account. We do not suspect that this should have a major effect on comparability of mean exposure concentrations with studies using imputation techniques.

The between-worker variability between companies and occupations constitutes the majority (70%) of the total variation in our measurements suggesting that a group based exposure characterisation of individuals is possible and feasibly by e.g. job exposure matrices for future use in epidemiological studies of the health effects of respirable quartz exposure.

Even though fixed effects, most importantly tools, explained only 13 % of the total variability and 20 % of the total between worker variability, there is still a potential for prevention by focusing on dust reducing tools and procedures.

Conclusion

This study shows that exposure concentration in 2018 in Denmark across a range of prevalent occupations with expected quartz exposure is well below the current occupational exposure limit. Use of power tools increases exposure concentration. Most of the variability in exposure concentration was seen between occupations and between companies.

Table 1. Grouping of occupations (ISCO88) [a], industries (NACE rev.2) [b], and tools among 140 quartz exposed persons, Denmark, 2018

Variables	Description
Occupation [a]	
7113	7113. Stonecutters and carvers
7122	7122. Bricklayers and stonemasons
7123	7123. Concrete placers, -finishers and related workers
7129	7129. Building frame and related trades workers
7220	7221. Blacksmiths, hammer-smiths and related workers
	7224. Metal wheel-grinders, polishers, sharpeners
8112	8112. Mineral, ore or stone processing-plant operators
8122	8122. Metal melters, casters and rolling-mill operators
8131	8131. Glass, ceramics kiln and related machine operators
8212	8212. Cement/other mineral products machine operators
8332	8332. Earth-moving- and related plant operators
9310	9312. Construction and maintenance labourers: roads, dams and similar constructions
	9313. Building construction labourers
Industry [b]	
08	081200: Operation of gravel and sand pits; mining of clays and kaolin
23	231400: Manufacture of glass fibres
	232000: Manufacture of refractory products
	233200: Manufacture of bricks, tiles and construction products, in baked clay
	236100: Manufacture of concrete products for construction purposes
	237000: Cutting, shaping and finishing of stone
24	245100: Casting of iron
25	256100: Treatment and coating of metals
41	412000: Construction of residential and non-residential buildings
42	421300: Construction of bridges and tunnels
	422100: Construction of utility projects for fluids
43	431100: Demolition
	431200: Site preparation
	439990: Other specialised construction activities
Tool	
None	No tool, computer, vacuum cleaner, spray gun
Hand tool	Hammer, saw, crowbar, wire binding tool, pliers, shovel, mursake
Power tool	Drill hammer, drill, angle grinder, bayonet saw, compressed air blow gun, mixing rod
Construction Machine	Wheel shovel, excavator, dumper truck, truck, road rollers, forklift,

[a] ISCO 88: International Standard Classification of Occupation, 1988 version

[b] NACE rev.2: European Classification of Industries, 2. version

Table 2. Characteristics, respirable dust and respirable quartz (µg/m^3) among 140 persons, Denmark, 2018

	Persons		Samples		Respirable dust µg/m^3		Quartz µg/m^3		Respirable dust µg/m^3			Quartz µg/m^3		
Characteristics	n	%	N	%	<LOD [a]	%	<LOD [b]	%	AM	GM	GSD [c]	AM	GM	GSD
Occupational group (ISCO88)														
7113. Stonecutters and carvers	10	7	15	8	0	0	0	0	1220	530	3.45	200	90	3.47
7122. Bricklayers and stonemason	17	12	24	13	0	0	9	38	280	140	2.81	60	20	4.36
7123. Concrete placers, -finishers and related	16	11	23	12	1	4	12	52	150	110	2.29	10	10	1.92
7129. Building frame and related trades workers	21	15	21	11	0	0	3	14	1550	720	2.95	60	30	2.95
7220. Blacksmiths, tool-makers and related	9	6	11	6	0	0	7	64	1040	720	2.50	20	10	4.78
8112. Mineral, ore or stone processing-plant operators	8	6	11	6	1	9	3	27	300	170	3.43	40	20	4.06
8122. Metal melters, casters and rolling-mill operators	10	7	18	10	0	0	0	0	1030	730	1.96	70	60	1.71
8131. Glass, ceramics kiln and related machine operators	17	12	22	12	1	5	10	45	380	240	3.05	20	10	2.26
8212. Cement/other mineral products machine operators	7	5	11	6	0	0	8	73	180	150	1.93	10	10	1.72
8332. Earth-moving- and related plant operators	10	7	14	7	6	43	10	71	30	20	2.48	10	0	n.r.
9310. Mining and construction labourers	15	11	19	10	2	11	9	47	150	90	3.16	20	10	2.49
Industry(NACE, rev.2)														
8. Other mining and quarrying	10	7	14	7	1	7	3	21	340	200	3.18	0.040	20	3.41
23. Manufacture of other non-metallic mineral products	34	24	48	25	1	2	18	38	580	270	3.25	0.070	20	4.81
24. Manufacture of basic metals	10	7	18	10	0	0	0	0	030	750	1.96	0.070	60	1.71
25. Manufacture of fabricated metal products, except machinery and equipment	7	5	8	4	0	0	7	88	200	890	2.45	0.010	0	3.75
41. Construction of buildings	7	5	14	7	0	0	11	79	140	110	2.12	0.020	0	3.85
42. Civil engineering	16	11	21	11	0	0	12	57	170	110	2.44	0.020	10	3.11
43. Specialised construction activities	56	40	66	35	9	14	20	30	690	170	5.65	0.040	20	3.58
Tool												0		
None	15	11	19	10	1	5	11	58	400	190	3.47	0.020	10	2.40
Use of hand tools	44	31	72	38	1	1	32	44	400	210	3.15	0.030	10	3.82
Use of power tools	40	29	46	24	0	0	8	17	1230	480	3.95	0.090	30	4.36
Operating construction machines	41	29	52	28	9	17	20	38	280	110	4.60	0.030	10	3.27
Location														
Indoor	68	49	93	49	1	1	27	29	910	500	3.05	0.060	20	3.82
Outdoor	72	51	96	51	10	10	44	46	310	120	3.82	0.030	10	4.11
Total	140	100	189	100	11	6	71	38	60	220	2.64	0.050	20	2.64

[a] Limit of Detection (LOD) for respirable dust = 25 µg, [b] Limit of Detection (LOD) for respirable quartz =10 µg, [c] GSD; Geometric standard deviation factor, n.r. not reported

Table 3. Determinants of respirable quartz level, 189 personal measurements among 140 workers, Denmark, 2018

	Exp(β)	95 % CI	p-value
Intercept	0.007	0.003-0.02	<0.001
Tool			
None (REF)	0.00		
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)	0.00		

Model excluding fixed effects: Occupation, company and worker as random effect
Model including fixed effects: Occupation, company and worker as random effect, tool, and location as fixed effects

Table 4. Variance components for respirable quartz level from models excluding and including fixed effects

	Variance components in model excluding fixed effects (%)	Variance components in model including fixed effects (%)
Total between workers variance	1.37 (70)	1.09 (63)
Between occupations variance	0.53 (27)	0.45 (26)
Within occupations, between companies variance	0.56 (29)	0.46 (27)
Within companies, between workers variance	0.28 (14)	0.18 (10)
Within worker variance	0.60 (30)	0.63 (37)
Total variance[1]	1.97 (100)	1.97 (100)
Sum of variance explained by random effects	1.97 (100)	1.72 (87)
Variance explained by fixed effects	-	0.25 (13)

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Paper II.

Boudigaard, SH, Schlünssen, V, Vestergaard, JM, Søndergaard, K, Torén, K, Peters, S, Kromhout, H, Kolstad, HA. Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases, a nationwide cohort study [*Accepted, International Journal of Epidemiology, 2020*]

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

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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 to 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 μg/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 μg/m^3-years).

Conclusion: 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.

Keywords: 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, rocks and in concrete, ceramics, glass and other industrial materials. Worldwide, a considerable number of especially male workers employed in construction, 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], while findings for women are unclear 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 affects people in the working age, women more often than men[25-29]. Low concordances between monozygotic twins indicates environmental factors to be 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 characterises 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 and materials

Study population

The study population comprised all Danish residents, born 1956 or later with a minimum of one 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 five years back. All Danish 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 [34] 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 (1977-1993) 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) [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 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 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 al 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 one year. We furthermore started follow up the earliest in 1979, two years after information on autoimmune rheumatic diseases was available from the National Patient Registry. We included this two-year washout period (1977-1978) 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 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 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 (1979-1984, 1985-1994, 1995-2004, 2005-2015). 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 were assigned the same smoking habit as for 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 homogenous 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, 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 strata is shown in supplementary table 3.

Among men, 17 % ever held a job with exposure to respirable crystalline silica while this was the case for three % of the women. Furthermore, women were lower exposed than men with median cumulative exposure of 33 µg/m^3-years (25 to 75 % centiles: 16 to 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 high 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 from 2005-2015 compared to 1979-1984, men have 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 was also indications of a latency effect of more than 20 years, however less evident than among men (Table 4).

In sub-analyses 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 1).

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 2). 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 2).

Discussion

Principal findings

Among men, we observed increasing risk of autoimmune rheumatic diseases following increasing occupational exposure to respirable crystalline silica. Findings were 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 relative 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 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 (SIR 2.59, 95 % CI 1.24, 4.76) at exposure levels of respirable crystalline silica above 50 µg/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, however, not observe an association between quantitative levels of silica exposure and rheumatoid arthritis in a cohort of pottery, sandstone and refractory material workers.

While 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 µg/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 disturbed control mechanism and breaking of tolerance result in continuous production of autoantibodies [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, autoantibodies are present years before clinical symptoms of systemic lupus erythematosus develops [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.

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Data availability

Data are not publicly available, but may be obtained from third party.

Conflicts of interest

None declared.

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

Disease	ICD 8 (1977-1993)	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 in seropositive and seronegative rheumatoid arthritis in ICD 10

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/m^3-years)				Cumulative respirable crystalline silica (µg/m^3-years)			
	0	2.0-29.2	29.3-93.9	94.0-1622	0	2.0-29.2	29.3-93.9	94.0-1622
Worker characteristics	28 596 448 Person-years	1 581 413 Person-years	1 644 508 Person-years	1 790 255 Person-years	30 957 666 Person-years	342 405 Person-years	280 298 Person-years	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[2]	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								
1979-1984	7	2	6	2	6	2	3	1
1985-1994	22	12	19	21	21	12	16	18
1995-2004	30	29	30	32	30	28	33	33
2005-2015	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

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

	Men										
	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)
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)*

Table 3. *(Continued)*

	Women										
	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)
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)*

[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 are shown in the tables. [c] Adjusted for age (≤25, 26-35,≥36) and calendar year (1979-1985, 1986-1995, 1996-2005, 2006-2015). n.r. not reported; cells with less than 5 cases

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

		Men											
		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)	
Cumulative exposure ($\mu g/m^3$-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 $\mu g/m^3$-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	0	31 276 025	4038	1	222	1	2986	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)	
	Per 50 $\mu g/m^3$-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 $\mu g/m^3$-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 ($\mu g/m^3$)													
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 $\mu g/m^3$			*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 $\mu g/m^3$			*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 $\mu g/m^3$			*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 ($\mu g/m^3$)													
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 $\mu g/m^3$			*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)*	
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 $\mu g/m^3$			*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 $\mu g/m^3$			*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)*	

Table 4. *(Continued)*

		Women									
		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)
Cumulative exposure ($\mu g/m^3$-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 $\mu g/m^3$-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 $\mu g/m^3$-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 $\mu g/m^3$-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 ($\mu g/m^3$)												
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 $\mu g/m^3$			*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 $\mu g/m^3$			*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)*
>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 $\mu g/m^3$			*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 ($\mu g/m^3$)												
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 $\mu g/m^3$			*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 $\mu g/m^3$			*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 $\mu g/m^3$			*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)*

[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 are shown in the tables. [c]Adjusted for age (≤25, 26-35, ≥36) and calendar year (1979-1985, 1986-1995, 1996-2005, 2006-2015). n.r. not reported; cells with less than 5 cases.

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

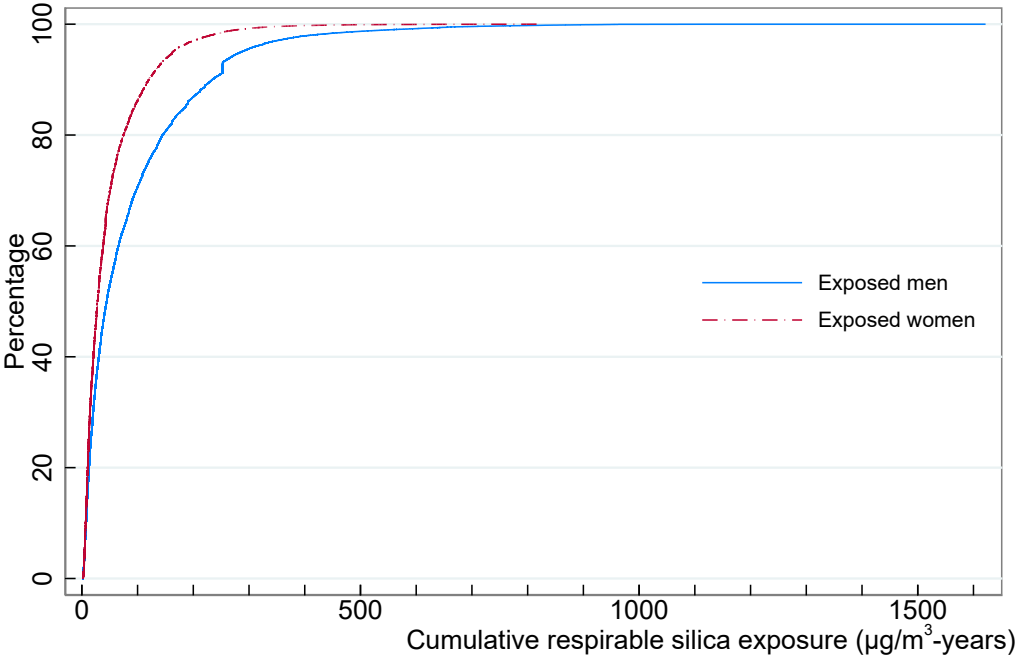
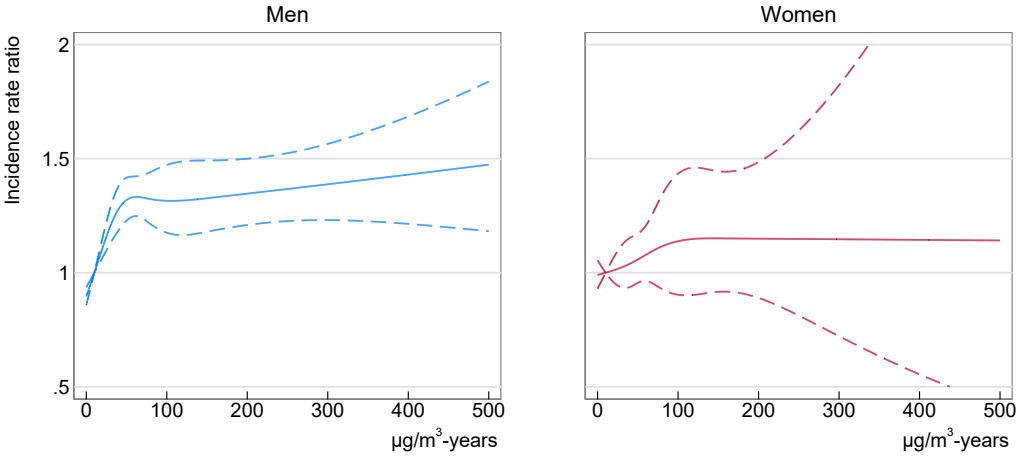


Figure 2. Restricted cubic spline fits of the age and calendaryear adjusted overall incidence rate ratios of autoimmune rheumatic diseases by cumulated respirable crystalline silica among 1 541 505 men and 1 470 769 women, 1979-2015



Supplementary table 1. Incidence rate ratios (IRR) of seropositive and seronegative rheumatoid arthritis following exposure to respirable crystalline silica among 1 541 505 men and 1 470 769 women, Denmark, 1979-20151979-2015

	Men					Women				
		Seropositive		Seronegative			Seropositive		Seronegative	
Exposure	Person-years	Cases	IRR[a] (95 % CI)	Cases	IRR[a] (95 % CI)	Person-years	Cases	IRR[a] (95 % CI)	Cases	IRR[a] (95 % CI)
Cumulative exposure ($\mu g/m^3$-years)										
0	28 567 899	1086	1	1357	1	30 865 519	3789	1	4657	1
2.0-29.2	1 579 301	101	1.31 (1.07-1.61)	108	1.16 (0.95-1.41)	341 276	45	0.82 (0.62-1.11)	64	0.98 (0.76-1.25)
29.3-93.9	1 641 890	123	1.49 (1.24-1.80)	133	1.37 (1.15-1.64)	279 261	56	1.21 (0.93-1.58)	50	0.93 (0.70-1.22)
94.0-1622	1 786 760	171	1.59 (1.35-1.88)	192	1.58 (1.36-1.85)	134 135	27	1.09 (0.75-1.59)	31	1.10 (0.77-1.57)
Per 50 $\mu g/m^3$-years			*1.08 (1.05-1.11)*		*1.07 (1.04-1.10)*			*1.05 (0.96-1.15)*		*1.03 (0.94-1.13)*
Per 50 $\mu g/m^3$-years (exposed only)			*1.03 (0.99-1.07)*		*1.02 (0.98-1.06)*			*1.06 (0.94-1.19)*		*1.06 (0.94-1.19)*
Mean exposure ($\mu g/m^3$)										
0	28 567 899	1086	1	1357	1	30 865 519	3789	1	4657	1
2.0-10.7	1 615 347	150	1.49 (1.26-1.77)	166	1.42 (1.21-1.67)	301,795	48	0.87 (0.65-1.15)	82	0.97 (0.76-1.24)
10.8-18.0	1 656 775	133	1.51 (1.26-1.81)	133	1.28 (1.07-1.54)	267,145	47	1.09 (0.81-1.45)	47	1.09 (0.84-1.42)
18.1-122.0	1 735 829	112	1.43 (1.17-1.73)	134	1.46 (1.22-1.75)	185,732	33	1.24 (0.88-1.75)	16	0.82 (0.56-1.22)
			2.51 (1.81-3.50)		*2.40 (1.76-3.27)*			*1.32 (0.75-2.31)*		*1.00 (0.58-1.75)*
			0.78 (0.38-1.59)		*1.31 (0.68-2.53)*			*2.06 (0.64-6.66)*		*1.33 (0.40-4.47)*
Highest attained exposure ($\mu g/m^3$)										
0	28 567 899	1086	1	1357	1	30 865 519	3789	1	4657	1
2.0-12.0	1 584 153	135	1.48 (1.23-1.77)	141	1.30 (1.10-1.55)	334 045	50	0.84 (0.64-1.11)	76	1.06 (0.84-1.33)
12.1-21.9	1 647 468	127	1.46 (1.21-1.75)	143	1.40 (1.18-1.66)	258 123	46	1.11 (0.83-1.49)	46	0.95 (0.71-1.28)
22.0-122	1 776 330	133	1.50 (1.25-1.80)	149	1.47 (1.24-1.74)	162 504	32	1.31 (0.92-1.85)	23	0.83 (0.55-1.25)
Per 50 $\mu g/m^3$			*2.08 (1.63-2.66)*		*1.99 (1.58-2.51)*			*1.26 (0.77-2.07)*		*1.00 (0.62-1.63)*
Per 50 $\mu g/m^3$ (exposed only)			*1.10 (0.68-1.76)*		*1.36 (0.87-2.11)*			*1.71 (0.61-4.77)*		*1.23 (0.43-3.49)*
Duration (years)										
0	28 567 899	1086	1	1357	1	30 865 519	3789	1	4657	1
1	975 669	49	1.14 (0.86-1.52)	53	1.01 (0.77-1.33)	210 968	29	0.92 (0.64-1.32)	39	1.03 (0.75-1.41)
2-5	1 996 483	129	1.38 (1.15-1.66)	157	1.41 (1.19-1.66)	364 080	57	0.98 (0.75-1.27)	65	0.95 (0.74-1.21)
6-39	2 035 799	217	1.66 (1.43-1.93)	223	1.51 (1.31-1.74)	179 624	42	1.18 (0.87-1.60)	41	1.00 (0.73-1.36)
Per year			*1.03 (1.02-1.04)*		*1.03 (1.02-1.04)*			*1.01 (0.99-1.04)*		*1.00 (0.98-1.03)*
Per year (exposed only)			*1.02 (1.00-1.03)*		*1.01 (0.99-1.02)*			*1.02 (0.98-1.06)*		*1.00 (0.96-1.04)*

[a] Adjusted for age (≤25, 26-35,≥36) and calendar year (1979-1985,1986-1995,1996-2005, 2006-2015)

Supplementary table 2. Incidence risk ratio (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 exposure among 1 541 505 Danish men when adjusting for probability of smoking, or adjusting for highest attained education or restricting analyses to 1 308 086 Danish men, working as blue collar workers at baseline

	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	cases	IRR (95 % CI)	cases	IRR (95 % CI)	cases	IRR (95 % CI)	cases	IRR (95 % CI)	cases	IRR (95 % CI)
1 541 505 men, adjusted for age, calendar year and smoking probability[c]											
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	1.15 (1.02-1.30)	8	0.63 (0.31-1.27)	218	1.15 (1.00-1.33)	18	1.41 (0.87-2.30)	46	1.27 (0.94-1.72)
29.3-93.9	1 639 692	351	1.31 (1.17-1.46)	14	0.94 (0.54-1.62)	267	1.31 (1.15-1.48)	16	1.19 (0.71-1.99)	57	1.45 (1.10-1.92)
94.0-1622	1 784 974	476	1.44 (1.31-1.59)	27	1.50 (0.99-2.26)	375	1.47 (1.32-1.64)	23	1.43 (0.92-2.22)	59	1.28 (0.98-1.69)
Per 50 µg/m^3-years			*1.06 (1.05-1.08)*		*1.09 (1.01-1.17)*		*1.06 (1.04-1.08)*		*1.08 (1.00-1.17)*		*1.05 (1.00-1.10)*
Per 50 µg/m^3-years (exposed only)			*1.04 (1.00-1.05)*		*1.11 (1.02-1.21)*		*1.02 (1.00-1.05)*		*1.07 (0.96-1.18)*		*0.99 (0.92-1.07)*
1 541 505 men, adjusted for age, calendar year and education[d]											
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	1.11 (0.98-1.25)	8	0.59 (0.29-1.20)	218	1.13 (0.98-1.30)	18	1.26 (0.78-2.06)	46	1.21 (0.89-1.64)
29.3-93.9	1 639 692	351	1.25 (1.12-1.40)	14	0.87 (0.50-1.50)	267	1.27 (1.11-1.44)	16	1.06 (0.63-1.77)	57	1.36 (1.03-1.80)
94.0-1622	1 784 974	476	1.37 (1.24-1.51)	27	1.37 (0.91-2.07)	375	1.40 (1.26-1.57))	23	1.31 (0.84-2.04)	59	1.23 (0.93-1.62)
Per 50 µg/m^3-years			*1.06 (1.03-1.07)*		*1.08 (1.00-1.16)*		*1.06 (1.04-1.08)*		*1.07 (0.99-1.16)*		*1.04 ()0.99-1.10*
Per 50 µg/m^3-years (exposed only)			*1.03 (1.01-1.06)*		*1.11 (1.02-1.22)*		*1.03 (1.00-1.05)*		*1.09 (0.98-1.20)*		*1.00 (0.93-1.08)*
Restricted to 1 308 086 men working as blue collar worker at baseline[e]											
Cumulative exposure (µg/m^3-years)											
0	25 519 083	3193	1	182	1	2348	1	183	1	525	1
2.0-29.2	1 500 720	271	1.25 (1.10-1.41)	8	0.73 (0.36-1.49)	208	1.26 (1.10-1.46)	17	1.39 (0.85-2.29)	44	1.35 (0.99-1.84)
29.3-93.9	1 591 052	340	1.41 (1.26-1.58)	14	1.08 (0.62-1.85)	258	1.42 (1.25-1.61)	16	1.23 (0.74-2.05)	55	1.50 (1.14-1.99)
94.0-1622	1 759 392	465	1.44 (1.30-1.59)	25	1.45 (0.94-2.22)	367	1.49 (1.33-1.67)	22	1.32 (0.84-2.08)	59	1.26 (0.95-1.65)
Per 50 µg/m^3-years			*1.06 (1.04-1.08)*		*1.08 (0.01-1.16)*		*1.06 (1.04-1.08)*		*1.07 (0.99-1.15)*		*1.04 (0.99-1.09)*
Per 50 µg/m^3-years (exposed only)			*1.01 (0.98-1.03)*		*1.09 (0.99-1.19)*		*1.01 (0.98-1.04)*		*1.04 (0.94-1.16)*		*0.97 (0.90-1.04)*

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 are shown in the tables.

c Adjusted for age (≤25, 26-35,≥36), calendar year (1979-1985, 1986-1995, 1996-2005, 2006-2015) and probability of smoking (5-25 %, 26-35 %, 36-74 %)

d Adjusted for age (≤25, 26-35,≥36), calendar year (1979-1985, 1986-1995, 1996-2005, 2006-2015 and highest attained educational level (primary, secondary or vocational, short cycle higher, medium cycle higher, long cycle higher education or unknown.)

e Blue collar worker: ISCO 88 codes 6000-9999 at baseline, Adjusted for age (≤25, 26-35,≥36) and calendar year (1979-1985, 1986-1995, 1996-2005, 2006-2015)

Supplementary table 3. Distribution of person years and persons in each exposure group in the analysis of all diseases combined following exposure to respirable crystalline silica among 1 541 505 men and 1 470 769 women, Denmark, 1979-2015

	Men		Women	
	Person-years[a]	Persons[b]	Person-years[a]	Persons[b]
Cumulative exposure (µg/m^3-years)				
0	28 527 938	1 511 232	30 800 795	1 466 108
2.0-29.2	1 576 698	239 793	340 301	41 329
29.3-93.9	1 639 692	162 452	278 490	20 893
94.0-1622	1 784 974	82 156	133 920	6 409
Mean exposure (µg /m^3)				
0	28 527 938	1 511 232	30 800 795	1 466 108
2.0-10.7	1 612 428	155 618	300 872	26 902
10.8-18.0	1 654 722	104 483	266 425	14 629
18.1-122.0	1 734 214	72 950	185 414	7 470
Highest attained exposure (µg /m^3)				
0	28 527 938	1 511 232	30 800 795	1 466 108
2.0-12.0	1 581 211	144 199	333 072	27 537
12.1-21.9	1 645 575	76 090	257 420	10 509
22.0-122	1 774 578	57 937	162 219	5 250
Duration (years)				
0	28 527 938	1 511 232	30 800 795	1 466 108
1	974 370	266 325	210 515	42 914
2-5	1 993 555	216 932	363 012	31 650
6-39	2 003 439	121 317	179 184	12 700

[a] Number of person-years for the analysis for of all studied diseases combined

[b] Persons can contribute to more than one exposure group during the follow up period, hence number does not add up to the total study participants

Paper III.

Boudigaard, SH, Stokholm, ZA, Vestergaard, JM, Mohr, MS, Søndergaard, K, Torén, K, Schlünssen, V, Kolstad, HA. A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases. *Occupational and Environmental Medicine. 2020; 77(2):64-69*

OPEN ACCESS

ORIGINAL RESEARCH

A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases

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ABSTRACT

Objectives Increased risk has been suggested for autoimmune rheumatic diseases following solvent exposure. The evidence for specific solvents is limited, and little is known about exposure–response relations. Styrene is an aromatic, organic solvent and the objective of this study was to analyse the association between occupational styrene exposure and autoimmune rheumatic diseases in men and women.

Methods We followed 72 212 styrene-exposed workers of the Danish reinforced plastics industry from 1979 to 2012. We modelled full work history of styrene exposure from employment history, survey data and historical styrene exposure measurements. We identified cases in the national patient registry and investigated gender-specific exposure–response relations by cumulative styrene exposure for different exposure time windows adjusting for age, calendar year and educational level.

Results During 1 515 126 person-years of follow-up, we identified 718 cases of an autoimmune rheumatic disease, of which 73% were rheumatoid arthritis. When adjusting for potential confounders and comparing the highest with the lowest styrene exposure tertile, we observed a statistically non-significantly increased risk of systemic sclerosis among women (incidence rate ratio (IRR)=2.50; 95% CI 0.50 to 12.50) and men (IRR=1.86; 95 % CI 0.50 to 7.00), based on 9 and 22 cases, respectively. Results were inconsistent for the other autoimmune rheumatic diseases examined.

Conclusion This study suggests an association between occupational styrene exposure and systemic sclerosis in men as well as in women but based on few cases. This is a new finding and has to be replicated before conclusions can be drawn.

Key messages

What is already known about this subject?
- Organic solvent exposure has been associated with systemic sclerosis and other autoimmune rheumatic diseases.

What are the new findings?
- This study suggests an association between occupational styrene exposure and systemic sclerosis.
- No consistent association was seen for rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis or Sjögren's syndrome.

How might this impact on policy or clinical practice in the foreseeable future?
- These findings highlight the possible role of work factors in systemic sclerosis.

Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome are autoimmune rheumatic diseases for which little is known about environmental risk factors.[1 2] Genetic predisposition is of importance; however, concordance rates among monozygotic twins is low and indicates that environmental factors play an important role in the aetiology of these diseases.[1 3] Smoking is a well-described risk factor for rheumatoid arthritis, and several epidemiological studies have linked occupational exposure to respirable quartz with systemic sclerosis, rheumatoid arthritis, small vessel vasculitis and systemic lupus erythematosus.[1 4]

The occurrence of systemic sclerosis has been associated with occupational exposure to trichloroethylene,[5 6] benzene, toluene or xylene,[7 8] major organic solvent categories[5–10] and unspecified solvents.[11] Exposure assessment has mainly relied on case-by-case expert assessment or job exposure matrices (JEMs) with few exceptions of self-reports.[6 11] Self-reported job tasks and JEM data have indicated associations between unspecified solvent exposure and rheumatic arthritis,[12–14] while the limited evidence for systemic lupus erythematosus is mainly negative.[15–17] Single studies have linked Sjögren's syndrome with aromatic and chlorinated solvents and small vessel vasculitis with unspecified solvent exposure.[18 19]

As it appears, there are little data on specific solvents. Some studies have assessed exposure–response relations based on semiquantitative exposure information, but none has included quantitative exposure information.[7–9 14 15 17 19] Thus, quantitative exposure data based on actual measurements of specific solvents will add significantly to the knowledge base about the suggested association between organic solvent exposure and autoimmune rheumatic diseases.

Styrene is an aromatic solvent with well-documented neurotoxic effects[20] and is possibly associated with lymphohaematopoietic malignancies[21 22] and non-malignant respiratory diseases.[23]

Styrene is a high-production-volume industrial chemical used as a monomer in the production of several plastic polymers and coatings.[20] High levels of styrene exposure are found in the work room air of the reinforced plastics industry during hand lamination of boats, wind mill rotor blades and other reinforced plastics products. Especially high exposure levels were seen before the 1990s.[24]

The aim of this study is to investigate the association between occupational styrene exposure and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome in men and women.

MATERIALS AND METHODS

Study population

A total of 456 Danish companies producing reinforced plastics products since the early 1960s were identified. In a national pension fund register of mandatory pension saving, all 77 491 workers ever employed in these companies between 1964 and 2007 were identified.[25] To have complete work histories, we excluded those with a registration in 1964 (3496 persons), the year the pension register was established. The Danish civil registration system provided information on vital status. We excluded 25 workers without information on vital status, as well as 1664 who died, disappeared or emigrated before begin of follow-up and 94 diagnosed with a rheumatic autoimmune disease before begin of follow-up as specified later. The study population then included 59 997 men and 12 215 women, in total 72 212 participants. Information on occupation for each year of employment in the study companies was obtained from Statistics Denmark[26] and coded according to the Danish version of the International Classification of Occupations (DISCO-88) into four categories: white collar (DISCO-88 codes 1000 to 5999), skilled blue collar (codes 6000 to 7999), unskilled blue collar worker (codes 8000–9999) and others (eg, student and retired workers).

Autoimmune rheumatic diseases

We identified cases of autoimmune rheumatic diseases in the National Patient Registry 1977–2012.[27] This registry holds information on all inpatient and outpatient contacts with any Danish public or private hospital since 1977. All contacts are registered according to the 8th version (ICD-8: 1977–1993) and 10th version (ICD-10: 1994–2012) of the International Classification of Diseases. Cases were defined as follows: systemic sclerosis: M340, M341, M342, M342A, M342B, M348, M348B, M349, 73400, 73401, 73402, 73408, 73409, 73491; rheumatoid arthritis: M050, M051, M051A-F, M052, M053, M058, M059, M060, M068, M069, 71219, 71229, 71238,71239; seropositive rheumatoid arthritis: M050, M051, M051A-F, M052, M053, M058, M059; seronegative rheumatoid arthritis: M060, M068, M069; systemic lupus erythematosus: M320, M321, M328, M329, 73419; small vessel vasculitis: M301, M310, M310A-B, M311, M311A, M313, M317, M318, M318A, M319, 22709, 44619, 44629, 44649, 44799, 44808, 44809 and Sjögren's syndrome: M350, 73 490.

Approximately 55% of cases were diagnosed at departments of rheumatology, otherwise at departments of dermatology, internal medicine or orthopaedic surgery. We defined incident cases as the first diagnosis of an autoimmune rheumatic disease during the study period with one exception: if different relevant diagnoses were recorded within a year, we selected the last because several hospital contacts may be needed before a confident diagnosis is established.[28] If more diagnoses were registered on the same day, we prioritised them as follows: systemic sclerosis, small vessel vasculitis, lupus erythematosus, Sjögren's syndrome and rheumatoid arthritis.

Exposure assessment

The exposure assessment included three steps: (A) estimation of styrene exposure intensity, (B) estimation of styrene exposure probability and (C) combining A and B into a styrene exposure score.

A. *Styrene exposure intensity* was modelled based on 1122 personal styrene measurements obtained from 133 Danish reinforced plastics companies between 1970 and 2011 and company information on main product, main process and calendar year.
B. *Styrene exposure probability* within the study population was modelled based on information from a job task survey performed 2013–2014 among 11 264 current or former workers in the industry since 1964. Of these, 4996 (43%) reported a job task implying direct styrene exposure. The odds of exposure for different worker characteristics (sex, occupation, year of employment) and company characteristics (main product and main process) were estimated in a mixed-effects logistic regression model.[22]
C. The predicted styrene exposure intensity and the styrene exposure probability were multiplied to get an individual styrene exposure score for each year a worker was employed in a study company.

Cumulated styrene exposure level was computed by adding the annual exposure scores from first to last year of employment during styrene production. For each worker, we also estimated the three components thereof: duration of employment during styrene production, mean styrene exposure intensity and mean styrene exposure probability.

Detailed information on the study population and exposure assessment is described elsewhere.[22 24 29]

Statistical methods

Follow-up started the year after the first year of employment during styrene production, at the earliest in 1979. Because the National Patient Registry began registration in 1977, we included a 2-year washout period (1977 to 1978) to reduce the number of prevalent cases. Follow-up ended at the date of first diagnosis of systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis, Sjögren's syndrome, death, emigration or end of follow-up on 31 December 2012.

Associations between styrene exposure and autoimmune rheumatic diseases were analysed with a multivariate logistic regression model with person-year as unit of analysis resulting in incidence rate ratios (IRRs) that we presented with 95% CIs.[30] We stratified all analysis on sex, which was decided a priori due to the higher prevalence of autoimmune rheumatic diseases among women.[31] We adjusted for age (≤39, 40–49, 50–59, 60–69, ≥70 years), education (secondary education, vocational education, short-cycle higher education, medium- or long-cycled higher education, unknown) and calendar year of follow-up (1979, 1980–1989, 1990–1999, 2000–2009, 2010–2012). The cumulated styrene exposure level was grouped in tertiles based on the total person-year exposure distribution of both sexes combined, resulting in three equally sized groups of low exposed (≤17 mg/m^3-years), medium exposed (18–67 mg/m^3-years) and high exposed (≥68 mg/m^3-years). Furthermore, we analysed separately duration of employment, mean styrene exposure probability and mean styrene exposure intensity as well as cumulative styrene exposure accrued during specified time windows

Table 1 Characteristics of person-years (percentages) according to cumulated styrene exposure level among 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

	Men			Women		
	Cumulated styrene exposure level (mg/m^3-years)			Cumulated styrene exposure level (mg/m^3-years)		
	≤17	18–67	≥68	≤17	18–67	≥68
Worker characteristics	367 861 person-years	438 164 person-years	456 872 person-years	137 002 person-years	67 056 person-years	48 171 person-years
Occupation*†						
White collar workers	20	14	16	37	28	25
Skilled blue collar workers	26	32	32	3	2	2
Unskilled blue collar workers	42	35	37	37	40	46
Others/unknown	12	19	15	23	30	27
Education*‡						
Secondary education	41	39	39	49	51	55
Vocational education	41	40	41	34	30	26
Short-cycle higher education	4	3	3	4	3	3
Medium-or long-cycle higher education	8	9	6	8	7	5
Unknown	6	9	11	5	9	11
Age (years by 1 November each year)						
≤39	43	32	28	40	32	26
40–49	28	28	26	29	28	26
50–59	19	23	24	19	23	24
60–69	8	12	15	9	12	16
≥70	2	5	7	3	5	8
Calendar year of follow-up*						
1979	1	2	2	1	2	2
1980–1989	9	21	28	11	23	28
1990–1999	22	32	33	24	30	34
2000–2009	50	35	29	48	35	29
2010–2012	18	10	8	16	10	7

*Age standardised.
†Grouped according to the Danish version of ISCO-88.
‡Highest completed education according to The Populations' Education Register (1981–2011).
ISCO-88, International Standard Classification of Occupations 1988.

(<5, 6–10, 11–15 and ≥16 years prior). In the latter analyses, we treated exposures within each window in separate models and classified styrene exposure outside the window as zero and dichotomised exposure level within the window by the median.[32] We estimated the log-linear relation with the original continuous variables. We used Stata V.13 for all statistical analysis.

RESULTS

The study population accumulated 1 515 126 person-years during follow-up. A total of 718 cases of autoimmune rheumatic diseases were identified between 1979 and 2012: systemic sclerosis (n=31), rheumatoid arthritis (n=527), systemic lupus erythematosus (n=38), small vessel vasculitis (n=80) and Sjögren's syndrome (n=42).

Table 1 shows person-year prevalences, age standardised worker characteristics and age by increasing cumulative styrene exposure for men and women. High cumulative styrene exposure was associated with higher age and follow-up during the 1970s–1980s, as expected. No consistent trends were seen for the other characteristics.

When adjusting for age, calendar year, educational level and comparing highest with lowest cumulative exposure tertile, we observed a non-significantly increased risk of systemic sclerosis among women (IRR=2.50; 95% CI 0.50 to 12.50) and men (IRR=1.86; 95% CI 0.50 to 7.00) (table 2). A trend of 1.19 (95 % CI 1.01 to 1.39) per 100 mg/m^3-years was seen for women, for men this value was 1.03 (95 % CI 0.94 to 1.13). Furthermore, among men, but not among women, we observed a non-significantly increased risk of rheumatoid arthritis when comparing high with low cumulative exposure (IRR=1.28; 95 % CI 0.96 to 1.70), with a trend of 1.02 (95 % CI 1.00 to 1.05) per 100 mg/m^3. We only tabulated the total number of cases to avoid cells with less than four cases.

Analyses of rheumatoid arthritis subclassified into seropositive and seronegative cases (information only available for ICD-10 codes) revealed an increased rate ratio of seropositive rheumatoid arthritis among high exposed women (IRR=1.95; 95 % CI 1.05 to 6.61) but not among high exposed men, and increased rate ratios of seronegative rheumatoid arthritis among high exposed men (IRR=1.52; 95 % CI 0.99 to 2.34) but not among women (table 3).

Risk of systemic sclerosis tended to increase with duration of employment, mean exposure intensity and mean exposure probability among women and less so among men (online supplementary table 1).

Analyses of cumulative styrene exposure accrued within different time windows indicated increasing risk of systemic sclerosis, rheumatoid arthritis and small vessel vasculitis following exposure received >10 years earlier among men. No such pattern was seen among women (online supplementary table 2).

Table 2 Incidence rate ratios with 95% CI for systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome by cumulated styrene exposure in 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

		Rate ratio			Rate ratio	
		Men			Women	
Styrene exposure level	n	Crude	Adjusted*	n	Crude	Adjusted*
Systemic sclerosis	22			9		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		2.52 (0.68 to 9.30)	1.90 (0.51 to 7.11)		1.02 (0.19 to 5.58)	1.15 (0.20 to 6.52)
≥68 mg/m^3-years		2.68 (0.74 to 9.75)	1.86 (0.50 to 7.00)		2.13 (0.48 to 9.53)	2.50 (0.50 to 12.50)
Per 100 mg/m^3-years		*1.05 (0.97 to 1.14)*	*1.03 (0.94 to 1.13)*		*1.18 (1.01 to 1.38)*	*1.19 (1.01 to 1.39)*
Reumatoid arthritis	359			168		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		1.32 (0.99 to 1.76)	1.12 (0.83 to 1.49)		0.93 (0.64 to 1.35)	0.83 (0.57 to 1.20)
≥68 mg/m^3-years		1.68 (1.28 to 2.21)	1.28 (0.96 to 1.70)		1.17 (0.80 to 1.71)	0.95 (0.63 to 1.41)
Per 100 mg/m^3-years		*1.04 (1.02 to 1.07)*	*1.02 (1.00 to 1.05)*		*1.05 (0.97 to 1.13)*	*1.01 (0.93 to 1.10)*
Systemic lupus erythematosus	23			15		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		0.94 (0.36 to 2.45)	0.84 (0.32 to 2.24)		1.28 (0.42 to 3.90)	1.50 (0.47 to 4.73)
≥68 mg/m^3-years		0.60 (0.21 to 1.74)	0.55 (0.18 to 1.66)		0.71 (0.15 to 3.35)	0.88 (0.18 to 4.35)
Per 100 mg/m^3-years		*0.70 (0.42 to 1.15)*	*0.68 (0.40 to 1.14)*		*0.65 (0.24 to 1.77)*	*0.71 (0.27 to 1.84)*
Small vessel vasculitis	61			19		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		1.01 (0.51 to 2.00)	0.82 (0.41 to 1.64)		0.79 (0.28 to 2.20)	0.71 (0.25 to 2.01)
≥68 mg/m^3-years		1.50 (0.80 to 2.81)	1.06 (0.55 to 2.04)		0.22 (0.03 to 1.67)	0.18 (0.02 to 1.38)
Per 100 mg/m^3-years		*1.06 (1.01 to 1.11)*	*1.03 (0.99 to 1.09)*		*0.39 (0.10 to 1.60)*	*0.32 (0.07 to 1.47)*
Sjögren's syndrome	18			24		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		0.42 (0.13 to 1.39)	0.40 (0.12 to 1.35)		1.10 (0.44 to 2.76)	1.01 (0.40 to 2.55)
≥68 mg/m^3-years		0.60 (0.21 to 1.74)	0.57 (0.19 to 1.70)		0.88 (0.29 to 2.68)	0.79 (0.25 to 2.52)
Per 100 mg/m^3-years		*0.75 (0.46 to 1.23)*	*0.74 (0.45 to 1.22)*		*0.77 (0.42 to 1.42)*	*0.73 (0.38 to 1.41)*

*Adjusted for age, calendar year of follow-up and educational level.

DISCUSSION

Our analyses suggested an association between styrene exposure and systemic sclerosis in men and women, but based on few observations. No consistent pattern was observed for the other autoimmune rheumatic diseases.

To our knowledge, this is the only study of styrene exposure and the occurrence of autoimmune rheumatic diseases. However, several earlier studies have suggested associations with exposure to aromatic and unspecified solvents. A recent meta-analysis reported an increased risk of systemic sclerosis following exposure to aromatic solvent (OR=2.72; 95% CI 1.21 to 6.09).[10] It has been argued that JEMs are less sensitive for women, resulting in risk estimates biased toward the null.[8 14] However, our styrene assessment provided sex-specific estimates, thus this should not apply to our results.

We relied on national company and pension registries and included a high proportion of all companies of the reinforced plastics industry since the 1960s and all workers ever employed in these companies, hence selection bias related to study population could hardly have affected our findings. The quantitative exposure assessment was based on personal styrene measurements and was independent of individual reporting and should

Table 3 Adjusted incidence rate ratios with 95% CI for seropositive* and seronegative† rheumatoid arthritis by cumulated styrene exposure level in 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

	Rate ratio‡ seropositive				Rate ratio‡ seronegative			
Styrene exposure level	n	Men	n	Women	n	Men	n	Women
	156		60		157		84	
≤17 mg/m^3 years		1		1		1		1
18–67 mg/m^3-years		1.19 (0.79 to 1.81)		0.89 (0.45 to 1.76)		1.17 (0.75 to 1.83)		0.97 (0.59 to 1.58)
≥68 mg/m^3‡-years		1.11 (0.73 to 1.70)		1.95 (1.05 to 6.61)		1.52 (0.99 to 2.34)		0.49 (0.24 to 0.98)
Per 100 mg/m^3-years		*0.98 (0.93 to 1.04)*		*1.11 (1.01 to 1.22)*		*1.04 (1.02 to 1.07)*		*0.87 (0.70 to 1.09)*

*Seropositive cases: ICD-10 codes: M050, M051, M051A-F, M052, M053, M058, M059.
†Seronegative cases: ICD-10 codes: M060, M068, M069.
‡Adjusted for age, calendar year of follow-up and educational level.
ICD-10, International Classification of Diseases, 10th version.

be unaffected by recall bias. Cumulative styrene exposure was a combination of styrene exposure intensity, probability and duration, each estimated with considerable uncertainty and this might have led to non-differential misclassification, underestimation of exposure–response relations and increased the risk of overlooking truly increased risks.

Outcomes were based on hospital register information obtained with a clinical purpose. A recent study showed a positive predictive value of 79% for a diagnosis of rheumatoid arthritis in the Danish National Patient Registry.[33] We had no similar information for systemic sclerosis obtained from the patient registry. Misclassification with 21% false positives will lead to attenuation of the association with styrene exposure. We classified cases by the first recorded diagnosis. Different rheumatic diseases often present with similar symptoms and clinical findings, and the first recorded diagnosis might be temporary[28] and probably often the most prevalent (rheumatoid arthritis). However, the diagnostic procedure is unlikely to be related to styrene exposure; hence the misclassification will be non-differential and most likely result in attenuation of risk estimates. Furthermore, we adjusted for calendar year of follow-up to account for changes in occurrence and diagnostic procedures and criteria over time.

Smoking is a well-documented risk factor for rheumatoid arthritis and possibly also for the other autoimmune rheumatic diseases.[1 34] We had no information on smoking that allowed us to adjust for this, but a previous smoking survey showed declining smoking prevalence with increasing duration of employment in this industry.[29] Thus, the increasing rate ratios seen for systemic sclerosis by cumulative styrene exposure are unlikely to be due to smoking.

In the reinforced plastics industry, acetone, a ketone, is a frequent co-exposure to styrene, but at low intensity.[35] Ketones have been related to systemic sclerosis in a few studies.[5 9] Respirable quartz, a strongly suggested risk factor for autoimmune rheumatic diseases is not found in this industry. Recent studies have suggested wood dust, that may be present in the reinforced plastics industry, as a risk factor for rheumatoid arthritis,[34] but this finding was not supported in another study.[36] Non-occupational styrene exposure from tobacco smoke or food is probably of minor importance.

Despite a large study population, we had low power to evaluate the association between styrene exposure and other autoimmune rheumatic diseases than rheumatoid arthritis as reflected in the wide CIs.

Our knowledge on the pathogenic mechanism behind autoimmune rheumatic diseases is far from complete. In a mouse model, styrene has been shown to increase levels of interleukins IL-4, IL-5, IL-13 and interferon-γ.[37] In systemic sclerosis IL-4 and IL-13 play a crucial role in differentiating T cells into T helper type 2 (Th2) cells as well as promoting fibrosis.[38] This strong Th2 response seems to be specific for systemic sclerosis and not present for the other autoimmune diseases.[38–40]

Whether our findings for systemic sclerosis can be generalised to other organic solvents than styrene is hard to say, because they comprise a wide range of chemicals with different toxicological profiles. To conclude this study suggests an association between occupational styrene exposure and systemic sclerosis but based on few cases. This is a new finding and has to be replicated before conclusions can be drawn. No consistent associations were observed for the other autoimmune rheumatic diseases.

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Full name of the PhD student: Signe Hjuler Boudigaard

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Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has taken part in planning the sampling strategy, including numbers of occupations and which occupations to be measured.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has recruited most of the companies. PhD student has taken part in most of the measurements at the worksite. PhD student has done the majority of datamanagement, and conducted the majority of analysis, supported by a statistician. PhD student has interpreted the data supported by the supervisors	
Drafting the manuscript:	A
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27.11.2020	Vivi Schlünssen	Vivi Schlünssen
27.11.2020	Henrik Kolstad	Henrik Kolstad

Date:

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Signature of the PhD student

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Signe Hjuler Boudigaard

This declaration concerns the following article/manuscript:

Title:	Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases, a nationwide cohort study
Authors:	Signe Hjuler Boudigaard, Vivi Schlünssen, Jesper Medom Vestergaard, Klaus Søndergaard, Kjell Torén, Susan Peters, Hans Kromhout, and Henrik A Kolstad

The article/manuscript is: Published ☐ Accepted ☒ Submitted ☐ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: International Journal of Epidemiology

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has taken part in planning the study design and methods.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has done datamanagement supported by at datamanager. PhD student has done analysis and interpretation of data supported by statistician and supervisors. Ph.d student has not taken part in elaborating the job exposure matrix used, nor the creation of the cohort	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** PhD student has drafted the manuscript	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
PhD student has submitted the manuscript and drafted the revision supported by the supervisors

Signatures of first- and last author, and main supervisor

Date	Name	Signature
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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Signe Hjuler Boudigaard

This declaration concerns the following article/manuscript:

Title:	A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases
Authors:	Signe Hjuler Boudigaard, Zara Ann Stokholm, Jesper Medom Vestergaard, Mette Skovgaard Mohr, Klaus Søndergaard, Kjell Torén, Vivi Schlünssen, Henrik A. Kolstad

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Boudigaard SH, Stokholm ZA, Vestergaard JM, Mohr MS, Søndergaard K, Schlünssen V o.a. A follow-up study of occupational styrene exposure and risk of systemic sclerosis, rheumatoid arthritis, and other systemic autoimmune rheumatological diseases. Occupational and Environmental Medicine. 2019 apr 1;76:A18. O2D.1. https://doi.org/10.1136/OEM-2019-EPI.47

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

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F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has taken part in planning the study design and methods.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has done datamanagement supported by at datamanager. PhD student has done analysis and interpretation of data supported by statistician and supervisors. Ph.d student has not taken part in elaborating the job exposure matrix used, nor the creation of the cohort	
Drafting the manuscript:	A

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Free text description of PhD student's contribution ***(mandatory)***
PhD student has drafted the manuscript

Submission process including revisions:	A
Free text description of PhD student's contribution ***(mandatory)***	
PhD student has submitted the manuscript and drafted the revision supported by the supervisors	

Signatures of first- and last author, and main supervisor

Date	Name	Signature
27.11.2020	Signe Hjuler Boudigaard	27/11-20 Signe Hjuler Boudigaard
27.11.2020	Henrik Kolstad	Henrik Kolstad

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