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Occupational Health

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

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

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

Key Messages

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

Introduction

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

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

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

Methods

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

Study population

The study population comprised all Danish residents, born 1956 or later, with a minimum of 1 year of gainful employment 1977–2015 and a valid job code according to the Danish version of the International Standard Classification of Occupations from 1988 (ISCO 88) as registered in the Danish Occupational Cohort (DOC*X).[33] DOC*X includes annual, harmonized information on employment and job code for all Danish citizens. The information is based on several data sources, such as union membership, self-report to the civil registration authorities, tax records and employers' mandatory reporting of occupation to Statistics Denmark of all employees.[33] If the ISCO code was missing in a year with active employment, we assigned the latest valid ISCO code up to 5 years back. All Danish citizens hold a unique social security number which is used by all official authorities and allows linkage with national registers. Through linkage with the national civil registration system'[4] we excluded those who died, disappeared or emigrated before the start of follow-up in 1979.

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

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

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

Autoimmune rheumatic diseases

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

Exposure assessment

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

Statistical methods

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

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

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

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

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

[b]Highest attained educational level.

(1979-84, 1985–94, 1995–2004, 2005–15). We did not have information on smoking at an individual level, but in supplementary analyses we used a smoking JEM developed for the DOC*X cohort used in this study.[40] This JEM provided sex- and calendar year-specific estimates of smoking prevalence for all ISCO 88 job codes, based on self-reported smoking habits reported in four large Danish population-based surveys. Years without employment were assigned the same smoking habit as in the latest job period. We furthermore conducted analyses adjusted for educational level (lower secondary, vocational or higher secondary, short-, medium- or long-cycle higher education, unknown) and analyses restricted to blue-collar workers (ISCO major categories 6–9) as defined at baseline, to

obtain a more homogeneous population with respect to smoking and socioeconomic factors.

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

Results

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

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

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

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

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

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

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

Discussion

Principal findings

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

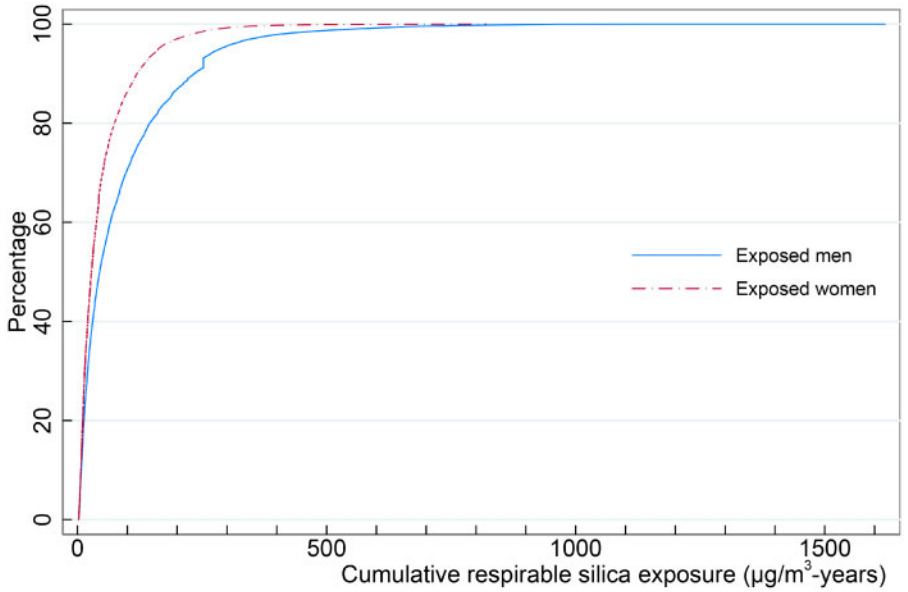

Figure 1 Cumulative plot of the distribution of cumulative exposure level (μg/m^3-years) at end of follow-up among 266 325 men and 42 914 women ever exposed to respirable crystalline silica

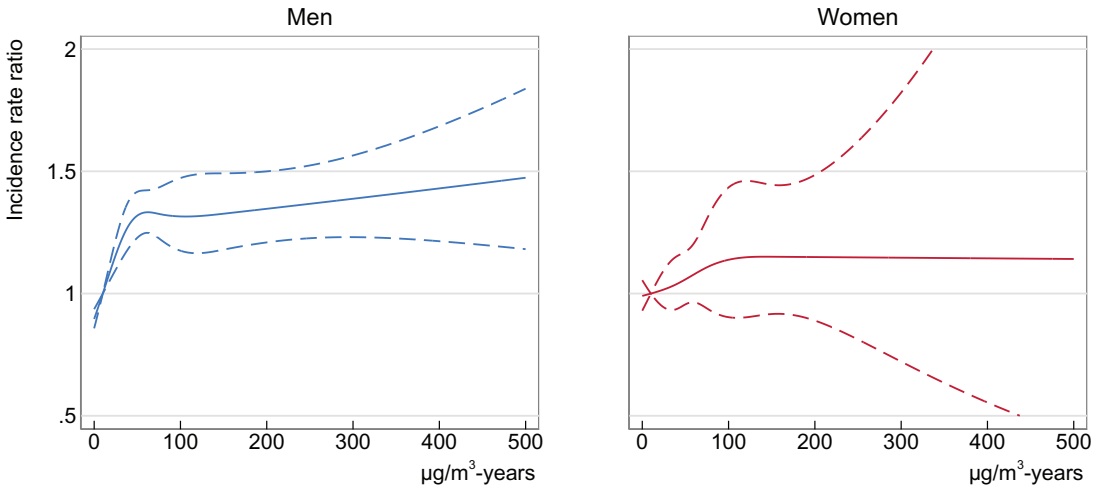

Figure 2 Restricted cubic spline fits of the age- and calendar year-adjusted overall incidence rate ratios of autoimmune rheumatic diseases by cumulated respirable crystalline silica among 1 541 505 men and 1 470 769 women, 1979–2015

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

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

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

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

(Continued)

Table 3. Continued

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

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

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

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

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

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

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

(Continued)

Table 4 Continued

Exposure	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)
12.6–121.9	1 922 876	257	1.21 (1.06–1.37)	20	1.39 (0.87–2.21)	185	1.23 (1.05–1.42)	15	1.19 (0.70–2.03)	39	1.01 (0.72–1.40)
Per 50 μg/m^3			1.91 (1.48–2.46)		1.69 (0.66–4.31)		2.08 (1.54–2.82)		1.78 (0.62–5.15)		1.40 (0.76–2.59)
11–20 years											
0	31 276 025	4038	1	222	1	2986	1	223	1	668	1
3.5–15.8	1 047 317	352	1.56 (1.39–1.74)	13	1.30 (0.74–2.31)	279	1.55 (1.37–1.76)	21	1.92 (1.21–3.04)	50	1.68 (1.25–2.27)
15.9–121.9	1 205 960	282	1.32 (1.17–1.49)	17	1.58 (0.95–2.61)	225	1.35 (1.18–1.55)	11	1.02 (0.55–1.88)	31	1.09 (0.76–1.57)
Per 50 μg/m^3			2.10 (1.72–2.57)		2.17 (0.91–5.00)		2.18 (1.74–2.74)		2.13 (0.89–5.11)		1.62 (0.91–2.89)
>20 years											
0	32 434 659	4242	1	230	1	3153	1	236	1	689	1
6.1–23.4	504 415	207	1.60 (1.39–1.84)	8	1.49 (0.72–3.08)	164	1.59 (1.35–1.86)	10	1.71 (0.89–3.27)	30	1.80 (1.23–2.62)
23.5–121.9	590 228	224	1.54 (1.34–1.77)	14	2.26 (1.29–3.95)	173	1.49 (1.27–1.74)	9	1.38 (0.70–2.73)	30	1.63 (1.12–2.37)
Per 50 μg/m^3			2.04 (1.71–2.44)		2.97 (1.41–6.25)		1.95 (1.60–2.39)		1.85 (0.77–4.42)		2.26 (1.40–3.66)
					Women						
Cumulative exposure (μg/m^3-years)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	854	1
2.0–37.1	319 807	134	0.98 (0.82–1.16)	10	1.26 (0.68–2.36)	93	0.89 (0.72–1.09)	24	1.23 (0.82–1.83)	10	1.08 (0.58–2.02)
37.2–875.2	182 463	68	0.97 (0.76–1.23)	5	1.08 (0.45–2.61)	52	1.00 (0.76–1.31)	7	0.65 (0.31–1.36)	5	1.00 (0.41–2.40)
Per 50 μg/m^3-years			1.00 (0.87–1.15)		0.92 (0.52–1.63)		1.00 (0.85–1.19		0.96 (0.67–1.38)		0.99 (0.60–1.65)
11–20 years											
0	31 252 372	12 085	1	732	1	9050	1	1798	1	n.r.	1
3.5–47.6	194 665	118	1.09 (0.91–1.31)	9	1.54 (0.79–2.97)	88	1.02 (0.83–1.26)	15	1.14 (0.69–1.90)	n.r.	1.40 (0.73–2.71)
47.7–875.2	106 469	65	1.08 (0.84–1.38)	5	1.51 (0.62–3.64)	52	1.08 (0.82–1.42)	8	1.14 (0.57–2.29)	n.r.	0.58 (0.14–2.31)
Per 50 μg/m^3-years			1.03 (0.92–1.16)		1.16 (0.75–1.77)		1.02 (0.89–1.17)		1.06 (0.76–1.48)		0.96 (0.56–1.65)
>20 year											
0	31 417 074	12 150	1	736	1	9096	1	n.r	1	n.r.	1
6.1–66.6	92 154	79	1.27 (1.01–1.58)	5	1.48 (0.61–3.57)	62	1.22 (0.95–1.57)	n.r	1.91 (1.08–3.38)	n.r.	1.09 (0.41–2.93)
66.7–1338.5	44 278	39	1.30 (0.95–1.78)	5	3.06 (1.27–7.40)	32	1.31 (0.92–1.85)	n.r	0.66 (0.17–2.65)	n.r.	1.69 (0.54–5.27)
Per 50 μg/m^3-years			1.12 (1.02–1.24)		1.36 (1.06–1.74)		1.14 (1.02–1.26)		1.15 (0.86–1.53)		1.13 (0.77–1.66)
Mean exposure (μg/m^3)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	n.r.	1
0.1–9.2	261 915	129	0.94 (0.82–1.16)	8	1.11 (0.55–2.23)	97	0.90 (0.74–1.10)	14	0.81 (0.478–1.37)	n.r.	1.57 (0.91–2.72)
9.3–122.0	240 355	73	1.03 (0.76–1.23)	7	1.31 (0.62–2.77)	48	0.98 (0.73–1.30)	17	1.30 (0.81–2.11)	n.r.	0.34 (0.08–1.35)
Per 50 μg/m^3			0.78 (0.39–1.55)		2.18 (0.31–15.40)		0.65 (0.28–1.54)		0.99 (0.21–4.57)		0.19 (0.1–3.64)
11–20 years											
0	31 252 372	12 085	1	n.r.	1	9050	1	1798	1	n.r.	1
0.1–8.1	128 933	83	1.11 (0.89–1.37)	5	1.23 (0.51–2.96)	65	1.09 (0.85–1.39)	10	1.14 (0.61–2.12)	858	0.33 (0.60–2.98)

(Continued)

Table 4 Continued

Exposure	The studied diseases combined[a]			Systemic sclerosis		Rheumatoid arthritis		Systemic lupus erythematosus		Small vessel vasculitis	
	Person-years[b]	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)	Cases	IRR[c] (95% CI)
8.2–110	172 201	100	1.07 (0.88–1.30)	9	1.77 (0.91–3.42)	75	1.01 (0.80–1.27)	13	1.14 (0.66–1.98)	6	0.93 (0.38–2.24)
Per 50 μg/m^3			1.24 (0.68–2.26)		5.37 (0.93–31.02)		1.03 (0.51–2.07)		1.30 (0.24–6.87)	5	0.28 (0.11–15.32)
>20 years											
0	31 417 074	12 150	1	n.r.	1	9096	1	1807	1	n.r.	1
0.2–11.7	54 240	50	1.37 (1.04–1.81)	n.r.	2.03 (0.76–5.43)	39	1.31 (0.96–1.80)	5	1.36 (0.56–3.28)	n.r.	1.89 (0.70–5.05)
11.8–110	82 192	68	1.21 (0.95–1.54)	n.r.	1.97 (0.88–4.42)	55	1.20 (0.92–1.57)	9	1.60 (0.83–3.09)	n.r.	0.91 (0.29–2.82)
Per 50 μg/m^3			1.91 (1.14–3.20)		4.79 (0.94–24.47)		1.95 (1.11–3.44)		3.30 (0.84–12.98)		1.11 (0.10–12.74)
Highest attained exposure (μg/m^3)											
1–10 years											
0	31 051 236	12 066	1	731	1	9045	1	1790	1	n.r.	1
2.0–12.5	311 925	148	0.97 (0.82–1.14)	9	1.10 (0.57–2.13)	109	0.91 (0.76–1.10)	20	0.99 (0.64–1.54)	n.r.	1.38 (0.79–2.38)
12.6–121.9	190 345	54	0.98 (0.75–1.29)	6	1.37 (0.61–3.08)	36	0.96 (0.69–1.34)	11	1.08 (0.59–1.95)	n.r.	0.42 (0.10–1.68)
Per 50 μg/m^3			0.83 (0.47–1.46)		1.63 (0.28–9.42)		0.73 (0.37–1.46)		0.93 (0.25–3.49)		0.40 (0.04–3.54)
11–20 years											
0	31 252 372	12 085	1	732	1	9050	1	1798	1	n.r.	1
3.5–15.8	183 189	114	1.04 (0.87–1.25)	8	1.37 (0.68–2.76)	87	0.99 (0.80–1.23)	15	1.19 (0.72–1.99)	n.r.	1.08 (0.51–2.28)
15.9–121.9	117 945	69	1.17 (0.92–1.48)	6	1.80 (0.80–4.02)	53	1.14 (0.87–1.49)	8	1.05 (0.53–2.11)	n.r.	1.17 (0.44–3.13)
Per 50 μg/m^3			1.29 (0.84–1.97)		2.90 (0.69–12.27)		1.18 (0.72–1.93)		1.62 (0.52–5.01)		1.26 (0.22–7.36)
>20 years											
0	31 417 074	12 150	1	n.r.	1	9096	1	1807	1	n.r.	1
6.1–23.4	84 633	73	1.26 (1.00–1.58)	n.r.	1.27 (0.47–3.40)	60	1.27 (0.98–1.64)	9	1.55 (0.80–2.99)	n.r.	1.16 (0.43–3.12)
23.5–121.9	51 799	45	1.31 (0.97–1.75)	n.r.	3.22 (1.44–7.21)	34	1.21 (0.86–1.70)	5	1.43 (0.59–3.45)	n.r.	1.50 (0.48–4.69)
Per 50 μg/m^3			1.66 (1.12–2.46)		4.13 (1.19–14.32)		1.62 (1.04–2.51)		2.52 (0.85–7.45)		1.75 (0.35–8.74)

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

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

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

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

prevalence via a smoking JEM; highest attained educational level; and in analyses restricted to blue-collar workers expected to have fairly comparable life style patterns across different occupations and silica exposure levels.

Comparison with other studies

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

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

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

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

Possible mechanisms

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

Conclusions

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

Supplementary data

Supplementary data are available at *IJE* online.

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Conflicts of interest

None declared.

References

1. Roney N, Faroon O, Williams M *et al. Toxicological Profile for Silica*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service: Agency for Toxic Substances and Disease Registry (ATSDR), 2019.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Arsenic, Metals, Fibres, and Dusts*. Lyon, France: IARC, 2012.

3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils*. Lyon, France: IARC, 1997.
4. T Mannetje A, Steenland K, Attfield M *et al.* Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med* 2002;**59**: 723–28.
5. Collis EL, Gu Y. The mortality experience of an occupational group exposed to silica dust, compared with that of the general population and an occupational group exposed to dust not containing silica. *J Indust Hyg* 1933;**15**:395–417.
6. Diot E, Lesire V, Guilmot JL *et al.* Systemic sclerosis and occupational risk factors: a case-control study. *Occup Environ Med* 2002;**59**:545–49.
7. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Male systemic sclerosis and occupational silica exposure - a population-based study. *Aust N Z J Med* 2000;**30**:215–20.
8. Marie I, Gehanno JF, Bubenheim M *et al.* Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014;**13**:151–56.
9. Blanc PD, Jarvholm B, Toren K. Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers. *Am J Med* 2015;**128**:1094–101.
10. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940-81. *Br Med J (Clin Res Ed)* 1987;**294**:997–1000.
11. Stolt P, Yahya A, Bengtsson C *et al.*; the EIRA Study Group. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. *Ann Rheum Dis* 2010;**69**:1072–76.
12. Turner S, Cherry N. Rheumatoid arthritis in workers exposed to silica in the pottery industry. *Occup Environ Med* 2000;**57**:443–47.
13. Vihlborg P, Bryngelsson IL, Andersson L, Graff P. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. *BMJ Open* 2017;**7**:e016839.
14. Yahya A, Bengtsson C, Larsson P *et al.* Silica exposure is associated with an increased risk of developing ACPA-positive rheumatoid arthritis in an Asian population: evidence from the Malaysian MyEIRA case-control study. *Mod Rheumatol* 2014;**24**(2):271–74
15. Ilar A, Alfredsson L, Wiebert P, Klareskog L, Bengtsson C. Occupation and risk of developing rheumatoid arthritis: results from a population-based case-control study. *Arthritis Care Res* 2018;**70**:499–509.
16. Cooper GS, Wither J, Bernatsky S; CaNIOS GenES Investigators *et al.* Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. *Rheumatology (Oxf)* 2010;**49**:2172–80.
17. Finckh A, Cooper GS, Chibnik LB *et al.* Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. *Arthritis Rheum* 2006;**54**:3648–54.
18. Parks CG, Cooper GS, Nylander-French LA *et al.* Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. *Arthritis Rheum* 2002;**46**:1840–50.
19. Gregorini G, Ferioli A, Donato F *et al.* Association between silica exposure and necrotizing crescentic glomerulonephritis with P-Anca and Anti-Mpo antibodies - a hospital-based case-control study. *Anca-Associated Vasculitides* 1993;**336**:435–40.
20. Hogan SL, Cooper GS, Savitz DA *et al.* Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. *CJASN* 2007;**2**:290–99.
21. Hogan SL, Satterly KK, Dooley MA *et al.* Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. *J Am Soc Nephrol* 2001;**12**:134–42.
22. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study. *Arthritis Rheum* 2003;**48**:814–23.
23. Nuyts GD, Van Vlem E, De Vos A *et al.* Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. *Nephrol Dial Transplant* 1995;**10**:1162–65.
24. Stratta P, Messuerotti A, Canavese C *et al.* The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. *Sci Total Environ* 2001;**270**:179–90.
25. Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;**390**:1685–99.
26. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;**376**:1094–108.
27. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet* 2014;**384**:1878–88.
28. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol* 2013;**17**:603–06.
29. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? *Best Pract Res Clin Rheumatol* 2005;**19**:191–207.
30. Gourley M, Miller FW. Mechanisms of disease: Environmental factors in the pathogenesis of rheumatic disease. *Nat Rev Rheumatol* 2007;**3**:172–80.
31. Selmi C, Leung PS, Sherr DH *et al.* Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. *J Autoimmun* 2012;**39**:272–84.
32. Wahren-Herlenius M, Dorner T. Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet* 2013;**382**:819–31.
33. Flachs EM, Petersen SEB, Kolstad HA *et al.* Cohort Profile: DOCX: a nationwide Danish occupational cohort with eXposure data—an open research resource. *Int J Epidemiol* 2019;**48**:1413–k.
34. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–25.
35. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90.
36. Peters S, Kromhout H, Portengen L *et al.* Sensitivity Analyses of Exposure Estimates from a Quantitative Job-exposure Matrix (SYN-JEM) for use in community-based studies. *Ann Occup Hyg* 2013;**57**:98–106.
37. Peters S, Vermeulen R, Portengen L *et al.* Modelling of occupational respirable crystalline silica exposure for quantitative exposure assessment in community-based case-control studies. *J Environ Monit* 2011;**13**:3262–68.

38. Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. *Occup Environ Med* 2010;**67**:67–71.
39. Checkoway H, Pearce N, Hickey JL, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health* 1990;**45**:95–100.
40. Bondo Petersen S, Flachs EM, Prescott EIB *et al.* Job-exposure matrices addressing lifestyle to be applied in register-based occupational health studies. *Occup Environ Med* 2018;**75**:890–97.
41. Ibfelt EH, Sorensen J, Jensen DV *et al.* Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. *Clin Epidemiol* 2017;**9**:627–32.
42. Butt SA, Jeppesen JL, Fuchs C *et al.* Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: a nationwide cohort study. *BMC Rheumatol* 2018;**2**:36.
43. Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of systemic lupus erythematosus and lupus nephritis in Denmark: a nationwide cohort study. *J Rheumatol* 2016;**43**:1335–39.
44. Miller FW, Alfredsson L, Costenbader KH *et al.* Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. *J Autoimmun* 2012;**39**:259–71.
45. Parks CG, Miller FW, Pollard KM *et al.* Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease. *Int J Mol Sci* 2014;**15**: 14269–97.
46. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. *Int Immunopharmacol* 2002;**2**:303–13.
47. Rubio-Rivas M, Moreno R, Corbella X. Occupational and environmental scleroderma. Systematic review and meta-analysis. *Clin Rheumatol* 2017;**36**:569–82.
48. Khuder SA, Peshimam AZ, Agraharam S. Environmental risk factors for rheumatoid arthritis. *Rev Environ Health* 2002;**17**:307–15.
49. Brown JM, Archer AJ, Pfau JC, Holian A. Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice. *Clin Exp Immunol* 2003;**131**:415–21.
50. European Parliament and the Council of the European Union, Official Journal of the European Union (L 345/87). DIRECTIVE (EU) 2017/2398 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Brussels: European Parliament and the Council of the European Union, 2017.
51. Pollard KM. Silica, silicosis, and autoimmunity. *Front Immunol* 2016;**7**:97.
52. Miller BG, Hagen S, Love RG *et al.* Risks of silicosis in coal-workers exposed to unusual concentrations of respirable quartz. *Occup Environ Med* 1998;**55**:52–58.
53. Eriksson C, Kokkonen H, Johansson M, Hallmans G, Wadell G, Rantapää-Dahlqvist S. Autoantibodies predate the onset of systemic lupus erythematosus in northern Sweden. *Arthritis Res Ther* 2011;**13**:R30.
54. Rantapää-Dahlqvist S, de Jong BAW, Berglin E *et al.* Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:2741–49.

Commentary: Silica—A Multisystem Hazard

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Silica has a long history. Inhalation of silica, a ubiquitous constituent of the Earth's crust in the form of quartz, produces the singular inflammatory and fibrotic lung disease we know as silicosis. The close association of pulmonary tuberculosis and silicosis as separate diseases was identified during the early years of the 20th century.[1] The nature of silica's association with lung cancer, an association accepted by the International Agency for Research on Cancer (IARC) in 2007, continues to be refined.[2] However, despite all our knowledge, epidemics of silica-related disease persist in both traditional and new industries, including in high-income countries.[3,4]

Identification and understanding of the role of silica in disease outside the lung have grown more slowly. Large mortality studies of silica-exposed populations have identified excess risk from renal disease[5] and cardiovascular disease.[6] Of growing interest has been the role of silica in multisystem disease, notably rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus (SLE), small vessel vasculitis and others, in which autoimmunity is the

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