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 4,673 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 μg/m³-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/m³-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

Introduction
Crystalline silica (SiO₂) 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. Since 1997, silica has been classified as a group 1 human lung carcinogen by the International Agency for Research on Cancer (IARC) and inhalation of fine particles of silica is furthermore a well-recognized risk factor for silicosis. A causal link of rheumatic diseases with occupational exposure to crystalline silica was already suggested from the 1930s. More recently, respirable crystalline silica has repeatedly been reported to increase the risk of several autoimmune rheumatic diseases: systemic sclerosis in men and women and rheumatoid arthritis in men; however, findings for women are unclear and based on few studies. Exposure to respirable crystalline silica may also increase the risk of systemic lupus erythematosus and small vessel vasculitis in men and women. These diseases affect people of working age, women more often than men. Low concordances between monozygotic twins indicate environmental factors as of aetiological importance. Thus we have much to learn about the complex pathogenesis, which potentially includes interaction between genetic, environmental and epigenetic factors.

Limited quantitative information on silica exposure levels characterizes most studies, and only few have examined exposure-response relations, 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). 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. 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, we excluded those who died, disappeared or emigrated before the start of follow-up in 1979.
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, 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). The SYNJEM originally provided time- and region-specific respirable crystalline silica exposure estimates for all job codes included in the 1968 version of ISCO, based on the modelling of 23,640 personal measurements of respirable crystalline silica from several European countries and Canada, together with expert assessments. For the current study, the SYNJEM was modified to provide exposure estimates for ISCO 88 job codes and was restricted to estimates for the Nordic countries. For each year of follow-up, we constructed the following exposure metrics based on each worker’s exposure history since entry: (i) cumulative exposure (µg/m³·year) as the sum of exposure levels for all exposed years; (ii) mean exposure intensity (µg/m³) as cumulative exposure divided by the number of exposed years; (iii) highest attained exposure intensity (µg/m³); 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). 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 terciles 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.

All analyses were stratified by sex and adjusted for age (≤25, 26–35, ≥36 years), and calendar year of follow-up.

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### 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, M3488, M349 |
| Rheumatoid arthritis        | 71219, 71229, 71238, 71239     | M05, M050, M051, M051A-F, M052, M053, M058, M059, M06, M060, M068, M069 |
| Seropositive rheumatoid arthritis |                             | M05, M050, M051, M051A-F, M052, M053, M058, M059 |
| Seronegative rheumatoid arthritis |                             | 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 |

*Rheumatoid arthritis is split into seropositive and seronegative rheumatoid arthritis in ICD 10.*
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. 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

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

| Worker characteristics | Men | | | | Women | | | |
|------------------------|-----|-----|-----|-----|-------|-----|-----|-----|
| Cumulative respirable crystalline silica (μg/m³-years) | Cumulative respirable crystalline silica (μg/m³-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 |
| 28,596,448 | 1,581,413 | 1,644,508 | 1,790,253 | 30,957,666 | 342,405 | 280,298 | 134,819 |

| Occupation | Men | | | | Women | | | |
|------------|-----|-----|-----|-----|-------|-----|-----|-----|
| 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 | Men | | | | Women | | | |
|-----|-----|-----|-----|-----|-------|-----|-----|-----|
| <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 | Men | | | | Women | | | |
|---------------|-----|-----|-----|-----|-------|-----|-----|-----|
| 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 | Men | | | | Women | | | |
|------------------------|-----|-----|-----|-----|-------|-----|-----|-----|
| 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 | 30 | 38 | 31 | 32 |
| Missing | 16 | – | – | – | 12 | – | – | – |

| Education | Men | | | | Women | | | |
|-----------|-----|-----|-----|-----|-------|-----|-----|-----|
| Lower secondary | 27 | 43 | 44 | 30 | 26 | 38 | 40 | 41 |
| Vocational or higher 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) | Men | | | | Women | | | |
|-----------------|-----|-----|-----|-----|-------|-----|-----|-----|
| 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 |

*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).

*Highest attained educational level.
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 4,673 cases of autoimmune rheumatic diseases during follow-up: systemic sclerosis (n = 252), rheumatoid arthritis (n = 3,490), 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 summed up to more than all autoimmune rheumatic diseases: systemic sclerosis (n = 746), rheumatoid arthritis (n = 9,190), systemic lupus erythematosus (n = 1,821) 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/m²-years (25-75% centiles: 16-72 μg/m²-years) versus 60 μg/m²-years (23-135 μg/m²-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 of the studied diseases.

Among men, we observed an increased overall incidence rate ratio 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/m³-years. The corresponding trend computed among the exposed only was 1.03 (95% CI: 1.00-1.05) per 50 μg/m³-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/m³-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
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, \(^4^1\) 94% for systemic sclerosis \(^4^2\) and 73% for systemic lupus erythematosus, when compared with medical records as the gold standard. \(^4^3\) 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 \(^4^4,4^5\) 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

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

**Figure 2** Restricted cubic spline fits of the age- and calendar year-adjusted overall incidence rate ratios of autoimmune rheumatic diseases by cumulative respirable crystalline silica among 1 541 505 men and 1 470 769 women, 1979–2015
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<sup>a</sup> | Systemic sclerosis | Rheumatoid arthritis | Systemic lupus erythematosus | Small vessel vasculitis |
|---------------------------------|------------------------------------------|--------------------|----------------------|-----------------------------|------------------------|
|                                 | Person-years<sup>b</sup> | Cases | IRR<sup>c</sup> (95% CI) | Cases | IRR<sup>c</sup> (95% CI) | Cases | IRR<sup>c</sup> (95% CI) | Cases | IRR<sup>c</sup> (95% CI) |
| Cumulative exposure (µg/m<sup>3</sup>-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<sup>3</sup>-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<sup>3</sup>-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<sup>3</sup>)| | | | | | | | | |
| 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<sup>3</sup>         | | | 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<sup>3</sup> (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<sup>3</sup>) | | | | | | | | | |
| 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) |
| 12.1–12.9                       | 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<sup>3</sup>         | | | 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<sup>3</sup> (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 | 1.36 (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)
| Exposure | Person-years | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) |
|----------|--------------|-------|---------------|-------|---------------|-------|---------------|-------|---------------|
| 0        | 30 800 795   | 11 888 | 176 | 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) |
| 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) |
| 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) |
| Per 50 μg/m³-years | | | | | | | | | |
| Women | | | | | | | | | |
| 1 | 0.09 (0.91–1.10) | 1.14 (0.95–1.36) | 1.05 (0.98–1.11) | 1.04 (0.89–1.22) | 1.03 (0.82–1.29) |
| Mean exposure (μg/m³) | | | | | | | | | |
| 0 | 30 800 795 | 11 888 | 176 | 1 | 8906 | 1 | 1767 | 1 | n.r. | 1 |
| 2.0–10.7 | 300 761 | 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) |
| 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 (0.92–2.01) |
| 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) |
| Per 50 μg/m³ | | | | | | | | | |
| Per 50 μg/m³ (exposed only) | | | | | | | | | |
| Per 50 μg/m³ | 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) |
| Highest attained exposure (μg/m³) | | | | | | | | | |
| 0 | 30 800 795 | 11 888 | 176 | 1 | 8906 | 1 | 1767 | 1 | 846 | 1 |
| 2.0–12.0 | 333 792 | 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) |
| 12.1–21.9 | 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) |
| 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) |
| Per 50 μg/m³ | | | | | | | | | |
| Per 50 μg/m³ (exposed only) | | | | | | | | | |
| Per 50 μg/m³ | 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) |
| Duration (years) | | | | | | | | | |
| 0 | 30 800 795 | 11 911 | 176 | 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) |
| 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) |
| 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) |
| Per 5 year | | | | | | | | | |
| Per 5 year (exposed only) | | | | | | | | | |
| 1 | 1.05 (0.97–1.14) | 1.19 (0.89–1.59) | 1.05 (0.95–1.15) | 0.99 (0.77–1.38) | 1.11 (0.81–1.51) |
| n.r. not reported, cells with less than five cases.

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

†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.

‡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* | Systemic sclerosis | Rheumatoid arthritis | Systemic lupus erythematosus | Small vessel vasculitis |
|---------------------------|--------------------------------|--------------------|----------------------|-------------------------------|------------------------|
|                           | Cases | IRR (95% CI)     | Cases | IRR (95% CI)     | Cases | IRR (95% CI)     | Cases | IRR (95% CI) |
| Per 50 μg/m³-years        |       |                  |       |                  |       |                  |       |              |
| Cumulative exposure (μg/m³-years) |       |                  |       |                  |       |                  |       |              |
| 1–10 years                | 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) |
|                           |       |                  |       |                  |       |                  |       |              |
|                           | 1.10 (1.04–1.16) | 1.07 (0.87–1.31) |       |                  |       |                  |       |              |
| Per 50 μg/m³-years        |       |                  |       |                  |       |                  |       |              |
| 11–20 years               | 31 276 025 | 4038 | 1 | 222 | 1 | 2986 | 1 | 223 | 1 | 668 | 1 |
| 0.35–47.6                 | 1 081 784 | 302 | 1.42 (1.27–1.60) | 16 | 1.64 (0.96–2.75) | 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) |
|                           |       |                  |       |                  |       |                  |       |              |
|                           | 1.13 (1.08–1.18) | 1.16 (0.97–1.38) |       |                  |       |                  |       |              |
| Per 50 μg/m³-years        |       |                  |       |                  |       |                  |       |              |
| >20 years                 | 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) | 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) |
| Mean exposure (μg/m³)     |       |                  |       |                  |       |                  |       |              |
| 1–10 years                | 29 829 503 | 3975 | 1 | 217 | 1 | 2953 | 1 | 217 | 1 | 650 | 1 |
| 0.1–9.2                   | 1 836 924 | 490 | 1.42 (1.28–1.56) | 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/m³              |       |                  |       |                  |       |                  |       |              |
| 11–20 years               | 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 | 1.53 (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 (0.66–2.40) | 212 | 1.34 (1.16–1.54) | 9 | 0.90 (0.46–1.76) | 36 | 1.38 (0.98–1.95) |
| Per 50 μg/m³              |       |                  |       |                  |       |                  |       |              |
| >20 years                 | 32 434 659 | 4242 | 1 | 230 | 1 | 3153 | 1 | 236 | 1 | 689 | 1 |
|                         |       |                  |       |                  |       |                  |       |              |
| Highest attained exposure (μg/m³) |       |                  |       |                  |       |                  |       |              |
| 1–10 years                | 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 | Person-years | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) |
|----------|--------------|-------|--------------|-------|--------------|-------|--------------|-------|--------------|
| 1.2–6 | 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) |
| Per 50 µg/m³ | 1 | | | | | | | | |
| 1–10 years | 31 276 025 | 4038 | | 222 | 1 | 2986 | 1 | 223 | 1 |
| >10 years | | | | | | | | | |
| 1.3–15.8 | 1 047 317 | 352 | 1.16 (1.00–1.37) | 13 | 1.30 (0.74–2.31) | 279 | 1.35 (1.17–1.76) | 21 | 1.92 (1.21–3.04) |
| Per 50 µg/m³ | 2.10 (1.72–2.57) | 2.17 (1.91–5.00) | 2.18 (1.74–2.74) | 2.13 (1.89–5.11) | 1.62 (0.91–2.89) |
| >20 years | 32 434 659 | 4242 | | 230 | 1 | 3153 | 1 | 236 | 1 |
| 1.4–23.4 | 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) |
| 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) |
| Per 50 µg/m³ | 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 (1.12–3.78) |

Women

Cumulative exposure (µg/m³-years)

| Exposure | Person-years | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) |
|----------|--------------|-------|--------------|-------|--------------|-------|--------------|-------|--------------|
| 1–10 years | 31 051 236 | 12 066 | 1 | 731 | 1 | 9045 | 1 | 1790 | 1 |
| >10 years | 31 252 372 | 12 085 | | 732 | 1 | 9050 | 1 | 1798 | 1 |
| 1.3–15.8 | 194 663 | 118 | 1.09 (0.91–1.31) | 9 | 1.54 (0.79–2.97) | 88 | 1.02 (0.83–1.26) | 15 | 1.14 (0.89–1.49) |
| Per 50 µg/m³-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 (0.67–1.38) |
| >20 years | 31 417 074 | 12 150 | | 736 | 1 | 9096 | 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) | 15 | 1.14 (0.89–1.49) |
| 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) | 15 | 0.66 (0.17–2.65) |
| Per 50 µg/m³-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/m³)

| Exposure | Person-years | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) | Cases | IRR* (95% CI) |
|----------|--------------|-------|--------------|-------|--------------|-------|--------------|-------|--------------|
| 1–10 years | 31 051 236 | 12 066 | 1 | 731 | 1 | 9045 | 1 | 1790 | 1 |
| >10 years | 31 252 372 | 12 085 | | 732 | 1 | 9050 | 1 | n.r. | 1 |
| 1.3–15.8 | 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 (0.47–1.37) |
| Per 50 µg/m³ | 0.78 (0.39–1.55) | 2.18 (0.31–1.54) | 0.65 (0.28–1.58) | 0.99 (0.21–4.57) | 0.19 (0.1–3.64) |
| >20 years | 31 252 372 | 12 085 | | n.r. | 1 | 9050 | 1 | 1798 | 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) |

(Continued)
Table 4 Continued

| Exposure          | Person-years<sup>b</sup> | Cases | IRR<sup>c</sup> (95% CI) | Person-years<sup>b</sup> | Cases | IRR<sup>c</sup> (95% CI) | Person-years<sup>b</sup> | Cases | IRR<sup>c</sup> (95% CI) | Person-years<sup>b</sup> | Cases | IRR<sup>c</sup> (95% CI) |
|-------------------|--------------------------|-------|--------------------------|--------------------------|-------|--------------------------|--------------------------|-------|--------------------------|--------------------------|-------|--------------------------|
| 8.2–110           | 172 201                  | 100   | 1.07 (0.88–1.30)         | 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<sup>3</sup> | 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         |                          |       |                         |                          |                   |                          |                          |                   |                   |
| 0.2–11.7          | 54 240                   | 50    | 1.37 (1.04–1.81)         | 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)         | 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<sup>3</sup> | 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<sup>3</sup>) |                   |       |                         |                          |                   |                          |                          |                   |                   |
| 1–10 years        |                          |       |                         |                          |                   |                          |                          |                   |                   |
| 0.2–12.5          | 310 512 236              | 12 066| 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)         |
| 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)         |
| Per 50 µg/m<sup>3</sup> | 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       |                          |       |                         |                          |                   |                          |                          |                   |                   |
| 0.2–12.5          | 31 252 372               | 12 085| 1.04 (0.87–1.25)         | 8                         | 1.37 (0.68–2.76)         | 87                        | 0.99 (0.80–1.32)         | 15               | 1.19 (0.72–1.99)         |
| 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)         |
| Per 50 µg/m<sup>3</sup> | 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         |                          |       |                         |                          |                   |                          |                          |                   |                   |
| 0.2–12.5          | 31 417 074               | 12 150| 1.10 (0.57–2.13)         | n.r.                      | 1.09 (0.76–1.57)         | 1807                      | 1.97 (0.88–4.42)         | 5 n.r. | 1.38 (0.79–2.38)         |
| 15.9–121.9        | 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 n.r. | 1.55 (0.80–2.99)         |
| Per 50 µg/m<sup>3</sup> | 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.

<sup>a</sup>The studied diseases combined: systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis.

<sup>b</sup>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.

<sup>c</sup>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.\textsuperscript{44,46} To our knowledge, only few studies have examined the association with quantitative exposure levels.\textsuperscript{12,13} Vihlborg et al.\textsuperscript{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).\textsuperscript{6,8,17,18} Turner et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{48} A single study on systemic lupus erythematosus found a higher risk among men than among women.\textsuperscript{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.\textsuperscript{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\(^3\),\textsuperscript{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.\textsuperscript{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.\textsuperscript{46,51} In susceptible individuals, a disturbed control mechanism and breaking of tolerance result in continuous production of auto-antibodies.\textsuperscript{32,51} Apoptosis of macrophages results in release of silica particles and new uptake by antigen-presenting cells, contributing to chronic inflammation.\textsuperscript{46} For silicosis it has been shown that most of the disease progression takes place after termination of exposure to crystalline silica.\textsuperscript{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,\textsuperscript{53,54} and it has been suggested that triggering exposures in susceptible individuals first lead to serological autoimmunity and later to overt clinical disease.\textsuperscript{52} 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.

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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. 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. However, despite all our knowledge, epidemics of silica-related disease persist in both traditional and new industries, including in high-income countries.

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 and cardiovascular disease. 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...