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Original research

Occupational exposure to respirable crystalline silica and incident idiopathic interstitial pneumonias and pulmonary sarcoidosis: a national prospective follow-up study

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ABSTRACT

Background Respirable crystalline silica is a well-known cause of silicosis but may also be associated with other types of interstitial lung disease. We examined the associations between occupational exposure to respirable crystalline silica and the risk of idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis.

Methods The total Danish working population was followed 1977–2015. Annual individual exposure to respirable crystalline silica was estimated using a quantitative job exposure matrix. Cases were identified in the Danish National Patient Register. We conducted adjusted analyses of exposure–response relations between cumulative silica exposure and other exposure metrics and idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis.

Results Mean cumulative exposure was 125 µg/m^3-years among exposed workers. We observed increasing incidence rate ratios with increasing cumulative silica exposure for idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis. For idiopathic interstitial pneumonias and pulmonary sarcoidosis, trends per 50 µg/m^3-years were 1.03 (95% CI 1.02 to 1.03) and 1.06 (95% CI 1.04 to 1.07), respectively. For silicosis, we observed the well-known exposure–response relation with a trend per 50 µg/m^3-years of 1.20 (95% CI 1.17 to 1.23).

Conclusion This study suggests that silica inhalation may be related to pulmonary sarcoidosis and idiopathic interstitial pneumonias, though these findings may to some extent be explained by diagnostic misclassification. The observed exposure–response relations for silicosis at lower cumulative exposure levels than previously reported need to be corroborated in analyses that address the limitations of this study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Respirable crystalline silica is a well-known cause of silicosis and associations with other types of interstitial lung disease have been suggested.

WHAT THIS STUDY ADDS

⇒ This study indicates that respirable crystalline silica may be associated with more types of interstitial lung disease than silicosis, including pulmonary sarcoidosis and idiopathic interstitial pneumonias.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings emphasise the need for further preventive initiatives for the millions of workers worldwide exposed to respirable crystalline silica.

INTRODUCTION

Interstitial lung diseases (ILDs) comprise a heterogeneous group of diseases characterised by inflammation or fibrosis of the pulmonary interstitium.[1] Some ILDs have known causes, among them pneumoconioses caused by inorganic dusts; hypersensitivity pneumonitis caused mainly by organic dusts; autoimmune-related ILDs and ILDs caused by drugs and radiation.[1] Idiopathic interstitial pneumonias, on the other hand, are per definition without any known cause, even though associations with several occupational dust exposures, smoking, viruses and drugs have been reported,[2–6] which challenges the relevance of a separate category of idiopathic ILDs.[6] Sarcoidosis is a granulomatous ILD which is also considered idiopathic, but recent evidence suggests associations with occupational exposures.[7 8] Clinical and radiological findings of ILDs with known causes and idiopathic ILDs are not pathognomonic, may overlap and in some cases be indistinguishable.[9 10]

Respirable crystalline silica has been a well-known cause of ILDs for centuries, and the risk of silicosis increases with increasing cumulative exposure to respirable crystalline silica.[11 12] Idiopathic interstitial pneumonias and sarcoidosis have also been associated with silica exposure.[2 8 13–15] The health implications of respirable crystalline silica exposure affect millions of workers worldwide in construction, agriculture, mining and metal manufacturing,

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where workers come into direct contact with soil and sand or process silica-containing products such as stone, concrete and glass.[16 17]

In this study, we examined the association between occupational exposure to respirable crystalline silica and idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis. We hypothesised that respirable crystalline silica exposure is associated with these types of ILD in an exposure-dependent manner.

METHODS

Study population

The study population is based on the Danish Occupational Cohort (DOC*X), which includes all residents of Denmark with at least 1 month of gainful employment from 1976 to 2015.[18] For years since 1976, DOC*X contains harmonised annual information on occupation, coded according to the 1988 International Standard Classification of Occupations (ISCO-88). We excluded workers born before 1900 or without at least 1 year of gainful employment. Within the total study population, we defined an inception population of all workers born 1956 or later with complete work histories since age 20 and a population restricted to blue-collar workers (ISCO-88 major categories 6–9) at baseline.

ILD subtypes

We identified incident cases of idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis in the Danish National Patient Register[19] which contains information on all inpatient contacts with Danish hospitals since 1977 and all outpatient contacts since 1995. Diagnoses were coded according to the 8th (1977–1993) and 10th (1994–2015) versions of the International Classification of Diseases (ICD-8 and ICD-10). ICD-8 codes were only available for silicosis.

We defined idiopathic interstitial pneumonias by ICD-10 code J84; pulmonary sarcoidosis by ICD-10 codes D86.0 and D86.2; and silicosis by ICD-8 code 515.0 and ICD-10 code J62. We included only pulmonary sarcoidosis as we expected crystalline silica to be a stronger risk factor for pulmonary sarcoidosis than other types of sarcoidosis.[20] The J84 code is labelled 'Other interstitial pulmonary diseases' in the ICD-10 classification, but it is standard national practice in Denmark to use this code mainly for the idiopathic interstitial pneumonias.

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias and has been the focus of many previous risk factor studies. Therefore, we did a subanalysis of IPF identified by ICD-10 code J84.1A.

Respirable crystalline silica exposure assessment

Exposure assessment was based on each individuals' work history as registered in DOC*X. When an ISCO-88 code was unknown for a certain year (13% of all employment years), we assigned the latest valid ISCO-88 code up to 5 years ago. We estimated individual quantitative respirable crystalline silica exposure for each year of employment using an ISCO-88 version of the job exposure matrix (JEM) SYN-JEM.[21 22] The original version of SYN-JEM contained annual exposure estimates for respirable crystalline silica for the more detailed ISCO-68 job codes by region/country, based on 23 640 personal exposure measurements from Europe and Canada. Recently, part of the exposure database was recoded to ISCO-88 codes and remodelled to create an ISCO-88 version of SYN-JEM. The ISCO-88 version of SYN-JEM is based on 15 204 personal exposure measurements as German measurements from the MEGA-database were not available.

We used the exposure estimates for Northern European countries to create the following exposure metrics for each worker: (1) cumulative exposure (μg/m^3-year) as the sum of the annual exposure intensities; (2) highest attained exposure intensity (μg/m^3) and (3) duration of exposure (years).

Statistical analyses

We started follow-up the year following the first year of employment, as no information on month or day of employment was available. For this reason, we also lagged all independent variables by 1 year. As the National Patient Register contains information on health outcomes dating back to 1977, we started follow-up for silicosis this year. For idiopathic interstitial pneumonias and pulmonary sarcoidosis, we started follow-up in 1994 when ICD-10 was introduced in Denmark. Each worker was eligible for inclusion in analyses of all three types of ILD, so for each analysis, we followed workers until the year of first relevant diagnosis (idiopathic interstitial pneumonias, pulmonary sarcoidosis or silicosis), death, emigration, disappearance or end of follow-up on 31 December 2015, whichever came first. Workers diagnosed with each disease before begin of follow-up were excluded from the respective analysis.

We analysed associations between respirable crystalline silica and the different types of ILD separately. We used a discrete time hazard model with person-years as a unit of analysis using logistic regression, yielding incidence rate ratios (IRRs) with 95% CIs.[23] For each exposure metric, person-years were first categorised as either exposed or non-exposed and the exposed group was then divided into tertiles based on the distribution of the exposed person-years. Exposure tertiles were based on the study population with begin of follow-up in 1977. Analyses were performed both for the total study population (with the non-exposed group as reference) and restricted to the exposed population (with the lowest exposed tertile as reference). Analyses were adjusted for age, sex, calendar year of follow-up, education, JEM estimates of smoking, previously diagnosed connective tissue disease, medication and previously diagnosed cancer. More information on the covariates is available in online supplemental material (appendix 1). For some analyses we reduced the number of covariates, as specified in the tables, to make the models fit. All variables were treated as time-varying accounting for the change in status and increase in cumulative exposure over time.

We fitted restricted cubic splines with 95% CIs for cumulative respirable crystalline silica as a continuous variable, placing the knots at the 5, 50 and 95 percentiles.[24] The most exposed 2.5% were omitted to focus on the most relevant results.

Exposure tertiles were recalculated for the inception population. Due to the smaller population size, it was not possible to repeat analyses restricted to the exposed group.

We used Stata V.17 (StataCorp) for all analyses.

The study was registered at the repository of the Central Denmark Region (j.no.: 1-16-02-196-17).

RESULTS

The total study population with begin of follow-up in 1977 comprised 5 439 728 workers with a total follow-up time of 141 508 223 person-years, while the population with begin of follow-up in 1994 comprised 5 100 706 workers with a total follow-up time of 88 145 471 person-years. Details of the establishment of the study population can be found in online supplemental figure S1.

We identified 17 869 cases of idiopathic interstitial pneumonias, 6670 cases of pulmonary sarcoidosis and 573 cases of silicosis. This corresponded to crude incidence rates per 100,000 person-years of 20.3 for idiopathic interstitial pneumonias, 7.6 for pulmonary sarcoidosis and 0.4 for silicosis.

10% of all person-years in the total study population were exposed to respirable crystalline silica (table 1). The most common exposed occupations were related to construction and farming which accounted for more than a third of all person-years contributed by the ever-exposed workers. The mean cumulative exposure was 125 μg/m^3-years and the mean duration of exposure 8.2 years among the exposed workers. High levels of cumulative silica exposure were associated with higher age, male sex, vocational or high secondary education and previous connective tissue disease and cancer.

In the total study population, we observed increasing IRRs for idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis with increasing cumulative respirable silica exposure with trends per 50 μg/m^3-years of 1.03 (95% CI 1.02 to 1.03), 1.06 (95% CI 1.04 to 1.07) and 1.20 (95% CI 1.17 to 1.23), respectively (table 2). Similar trends were seen when excluding the non-exposed groups. IRRs for the highest exposure group (the highest tertile) compared with the non-exposed group were 1.14 (95% CI 1.08 to 1.21), 1.61 (95% CI 1.45 to 1.78) and 2.95 (95% CI 2.31 to 3.76) for idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis. The risk of idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis increased with increasing duration of exposure. Risk patterns were less clear for the highest attained exposure.

Estimates only adjusted for age and sex are shown in online supplemental table S1.

Spline analyses showed monotonic increase in risk of idiopathic interstitial pneumonias and silicosis with increasing cumulative respirable crystalline silica exposure while the risks of pulmonary sarcoidosis increased up to around 200 μg/m^3-years where it levelled off at about a doubled risk (figure 1).

In the inception population, we observed increasing risks with increasing cumulative respirable silica exposure for idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis (IRR 1.05 (95% CI 1.02 to 1.08), 1.07 (95% CI 1.05 to 1.10) and 1.26 (95% CI 1.17 to 1.36) per 50 μg/m^3-years, respectively) (online supplemental table S2). The risk of silicosis also increased with increasing highest attained exposure while the risk of idiopathic interstitial pneumonias and pulmonary sarcoidosis increased with increasing duration of exposure.

In analyses restricted to blue-collar workers (online supplemental table S3), we observed patterns largely similar to those for the entire study population for pulmonary sarcoidosis and silicosis. For idiopathic interstitial pneumonias, no increasing risk with increasing exposure was observed.

In a subanalysis of IPF, we observed an IRR of 1.01 (95% CI 0.97 to 1.06) per 50 μg/m^3-years, but the IRRs did not increase consistently with increasing exposure tertile (online supplemental table S4).

More than 80% of all exposed person-years in the total study population were accrued in occupations belonging to agriculture and construction (online supplemental table S5). Less than 1% of exposed person-years was related to work in quarries and stone-processing.

DISCUSSION

In this study, we observed increasing risks of pulmonary sarcoidosis, idiopathic interstitial pneumonias and silicosis with increasing cumulative respirable crystalline silica exposure.

The consistent association observed between crystalline silica exposure and pulmonary sarcoidosis agrees with several previous studies.[7 8 13 14] Graff *et al*[13] observed an exposure–response relation between exposure duration and sarcoidosis. In contrast to earlier studies, however, our outcome is limited to pulmonary sarcoidosis.

An association for idiopathic interstitial pneumonias was observed in analyses of the total and inception population. Previously, a doubled risk following silica exposure was reported in a meta-analysis of four studies by Taskar *et al*[2] and a fivefold increase in a study by Kim *et al*.[15] Weaker associations have also been reported,[3 4] as well as no association.[5] None of these studies quantified silica exposure, and all studies, except Kim *et al*, investigated the association for IPF only and not idiopathic interstitial pneumonias in general. In a subanalysis, we did not find an increased risk of IPF.

Previous studies have established an exposure–response relation between cumulative respirable crystalline silica exposure and silicosis, but these studies have predominantly focused on a few occupations with high exposure levels, such as miners and diatomaceous earth workers.[12 25] In this study, we observed increased risk of silicosis at exposure levels significantly lower than those typically reported in prior studies, and also well below the cumulative exposure of 1000 μg/m^3-years which would be acquired during 10 years of work at the current European Union workplace exposure limit of 100 μg/m^3. However, a study of a cohort of industrial sand workers found a 22% increased mortality of silicosis and unspecified pneumoconiosis (as one common outcome category) for cumulative exposure levels >100 to 510 μg/m^3-years compared with >0 to 100 μg/m^3-years,[26] thus corroborating our findings at low exposure levels. Nevertheless, our cohort differs considerably from previous cohorts, as the majority of exposed person-years were accrued in the construction and farming industries where the risk of silicosis has been studied to a very limited extent.[27 28]

The mechanism by which silica induces pulmonary fibrosis is not fully understood.[29 30] When inhaled, crystalline silica particles reach the alveoli where they are phagocytosed by macrophages, thereby inducing secretion of proinflammatory substances. This, in turn, stimulates a profibrotic response with fibroblast activation, collagen secretion and subsequent fibrosis.[29 30] Our findings suggest that silica inhalation leads to lung injury that may be related to more clinical and radiological findings than those traditionally attributed to silicosis.

Strengths and limitations

We studied the total Danish working population, which allowed us to study these relatively rare diseases. Some patients with minor symptoms may not be referred to hospitals, but we do not expect the likelihood of referral to be associated with exposure status as healthcare in Denmark is universal with no user payment. All diagnoses were retrieved from the National Patient Register, which is used extensively for epidemiological research. We do not know the diagnostic process leading to each diagnosis, but in Denmark, ILDs are diagnosed by specialists in pulmonology at four national ILD centres, meaning that the quality of the register data is likely high. Furthermore, a high validity of diagnoses of other pulmonary diseases,[31] as well as a wide

Table 1 Distribution of person-years at risk (%) by time-varying worker characteristics and cumulative respirable crystalline silica level among 5 439 728 workers, Denmark, 1977–2015

	Cumulative respirable crystalline silica (μg/m^3-years)			
	0	<43.6	43.6–153.1	>153.2
	127 412 176	4 676 798	4 675 378	4 743 871
Worker characteristics	Person-years	Person-years	Person-years	Person-years
Sex				
Male	48.6	83.3	90.4	96.6
Female	51.4	16.7	9.6	3.4
Occupation*				
Armed forces	0.7	0.5	0.3	0.1
White-collar workers	46.8	16.2	9.5	7.3
Skilled blue-collar workers	8.2	17.7	18.2	34.6
Unskilled blue-collar workers	13.5	42.8	44.7	25.0
Unemployed or retired	23.3	21.2	24.6	25.5
Missing	7.5	1.5	2.7	7.4
Age				
<20	5.7	3.2	1.0	0.0
20–24	9.9	9.9	4.5	1.6
25–29	10.2	12.3	7.4	3.8
30–34	10.4	12.3	9.5	5.9
35–39	10.2	11.9	10.7	8.0
40–44	9.7	10.9	11.0	9.9
45–49	9.0	9.7	10.3	11.2
50–54	8.2	8.2	9.3	11.4
55–59	7.4	7.0	8.6	11.1
60–64	6.3	5.6	8.0	10.6
65–69	5.1	4.1	6.9	9.3
70–74	3.6	2.6	5.4	7.3
75–79	2.3	1.4	3.8	5.1
≥80	2.0	1.1	3.5	4.6
Calendar year				
1979–84	15.7	8.4	13.1	3.8
1985–94	25.6	14.9	31.0	26.6
1995–2004	27.5	28.0	25.7	35.1
2005–15	31.2	48.7	30.3	34.4
Probability of smoking				
5%–30%	34.3	35.8	19.9	18.3
31%–50%	32.2	39.6	32.3	57.1
51%–74%	33.5	24.6	47.8	24.6
Education†				
Unknown	7.7	5.7	11.6	5.5
Lower secondary	31.7	47.8	51.5	39.0
Vocational or high secondary	39.3	37.8	32.2	51.7
Short cycle higher	3.3	2.4	1.8	1.6
Medium cycle higher	12.7	4.5	2.3	1.9
Long cycle higher	5.2	1.8	0.6	0.3
Connective tissue disease				
No	99.0	99.3	99.1	98.8
Yes	1.0	0.7	0.9	1.2
Cancer				
No	97.1	97.8	97.3	96.2
Yes	2.9	2.2	2.7	3.8
Medication				
No	97.3	97.9	98.4	97.8
Yes	2.7	2.1	1.6	2.2
Duration of exposure (years)				
0	100.0	0.0	0.0	0.0

continued

Table 1 continued

	Cumulative respirable crystalline silica (µg/m^3-years)			
1–2	0.0	66.1	13.6	0.0
3–8	0.0	32.8	63.8	22.7
9–39	0.0	1.2	22.6	77.3

*Grouped according to International Standard Classification of Occupations (ISCO), 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.

range of other diseases,[32–34] has previously been observed, though the validity of ILD diagnoses has not been studied. We chose only to define pulmonary sarcoidosis by ICD-10 codes with specific mention of pulmonary involvement. Not all cases of pulmonary sarcoidosis are registered using these specific codes, meaning that we may have missed some cases, but those that are included will have pulmonary involvement with a high degree of certainty.

Diagnostic misclassification between ILD subtypes may have affected our results, as there are radiological and histological similarities between silicosis and other types of ILD, such as idiopathic interstitial pneumonias and sarcoidosis.[35] A detailed history of occupational exposures is part of the diagnostic programme at the Danish ILD centres, but previous silica exposure could potentially be missed in some cases, leading to actual cases of silicosis being classified as other types of ILD. Thus, diagnostic misclassification may to some extent explain the increased risks observed for idiopathic interstitial pneumonias and sarcoidosis in this study.

ILDs are a relatively rare group of diseases and age at onset is often high. Therefore, in order to identify a sufficient number of cases for all types of ILD, we included persons in our study population who had worked prior to our earliest information on occupation. Workers who held a job at baseline may constitute a healthier survivor population compared with all people who worked prior to follow-up, which may lead to bias towards the null.[36] To account for this issue, we repeated our analyses in the inception population born in 1956 or later with a complete work history since age 20. Even though the lower number of cases led to greater statistical uncertainty of the estimates, the overall risk patterns were largely unchanged, supporting the validity of the findings of the primary analyses.

We estimated individual exposure levels using a quantitative JEM which allowed us to perform exposure–response analyses crucial for investigation of causality. A JEM-assigned exposure is subject to non-differential misclassification because the JEM does not allow for variation in exposure within an occupation, but it will mainly lead to Berkson-type

Table 2 Incidence rate ratios (IRR) of idiopathic interstitial pneumonias (IIPs), pulmonary sarcoidosis and silicosis following exposure to respirable crystalline silica (RCS) as assessed by a job exposure matrix, Denmark

	IIPs*		Pulmonary sarcoidosis*		Silicosis†	
Exposure to RCS	**Cases**	**IRR (95% CI)‡**	**Cases**	**IRR (95% CI)‡**	**Cases**	**IRR (95% CI)‡**
Cumulative exposure (µg/m^3-years)						
0	14 972	1	5527	1	369	1
<43.6	612	1.04 (0.96 to 1.13)	397	1.30 (1.17 to 1.44)	29	1.45 (0.99 to 2.13)
43.6–153.1	831	1.15 (1.07 to 1.23)	332	1.58 (1.41 to 1.76)	79	1.86 (1.45 to 2.39)
153.2–1300	1454	1.14 (1.08 to 1.21)	414	1.61 (1.45 to 1.78)	96	2.95 (2.31 to 3.76)
Per 50 µg/m^3-years, including non-exposed		1.03 (1.02 to 1.03)		1.06 (1.04 to 1.07)		1.20 (1.17 to 1.23)
Per 50 µg/m^3-years, excluding non-exposed§		1.03 (1.01 to 1.04)		1.03 (1.01 to 1.05)		1.16 (1.12 to 1.20)
Highest attained exposure (µg/m^3)¶						
0	14 972	1	5527	1	369	1
<13.8	726	1.11 (1.03 to 1.20)	486	1.34 (1.22 to 1.47)	27	2.31 (1.55 to 3.45)
13.8–22.4	491	1.13 (1.03 to 1.23)	199	1.65 (1.43 to 1.90)	40	2.45 (1.76 to 3.40)
22.5–105.4	1680	1.12 (1.06 to 1.18)	458	1.57 (1.42 to 1.74)	137	2.34 (1.91 to 2.86)
Per 5 µg/m^3, including non-exposed		1.03 (1.02 to 1.03)		1.05 (1.04 to 1.07)		1.18 (1.16 to 1.21)
Per 5 µg/m^3, excluding non-exposed§		1.04 (1.02 to 1.05)		1.02 (1.00 to 1.04)		1.23 (1.19 to 1.27)
Duration (years)¶						
0	14 972	1	5527	1	369	1
1–2	428	1.06 (0.96 to 1.17)	241	1.23 (1.08 to 1.41)	43	2.24 (1.63 to 3.07)
3–8	929	1.15 (1.08 to 1.23)	383	1.43 (1.29 to 1.59)	89	2.29 (1.81 to 2.90)
9–39	1540	1.12 (1.06 to 1.18)	519	1.67 (1.52 to 1.83)	72	2.54 (1.94 to 3.34)
Per 5 years, including non-exposed		1.03 (1.01 to 1.05)		1.17 (1.14 to 1.20)		1.33 (1.22 to 1.44)
Per 5 years, excluding non-exposed§		1.00 (0.97 to 1.03)		1.10 (1.05 to 1.14)		1.09 (0.94 to 1.25)

*Followed from 1994 to 2015, 5 100 706 workers.
†Followed from 1977 to 2015, 5 439 728 workers.
‡Adjusted for age, sex, calendar year, education, probability of smoking, connective tissue disease, cancer and medications.
§For silicosis: not adjusted for education.
¶For silicosis: all analyses for this metric are not adjusted for education.

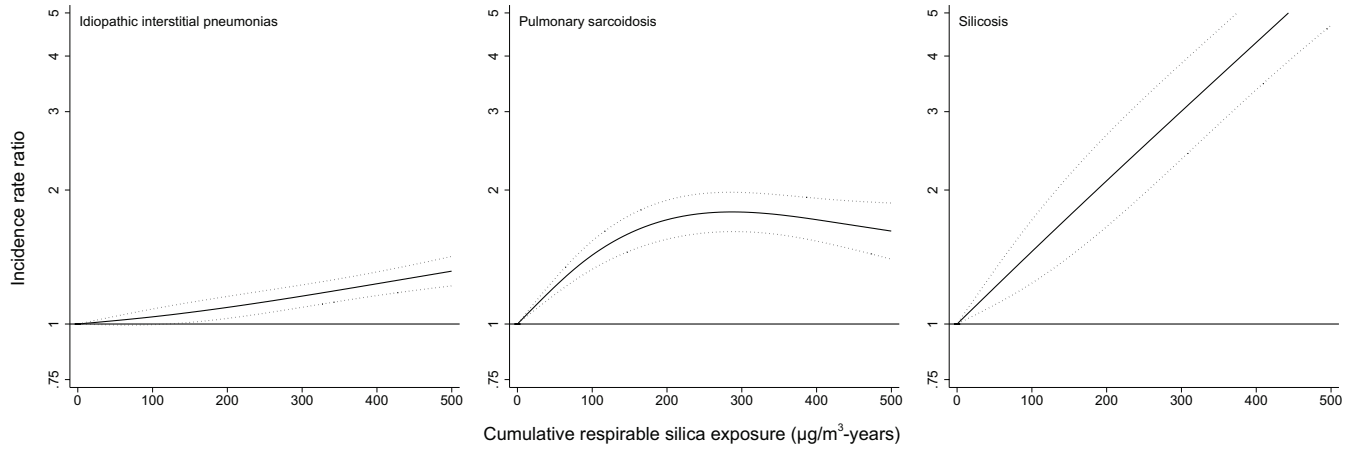

Figure 1 Restricted cubic spline fits of adjusted incidence rate ratios of idiopathic interstitial pneumonias, pulmonary sarcoidosis and silicosis by cumulative respirable crystalline silica. Dotted lines mark 95% CIs.

error, which will increase uncertainty of the risk estimates but not attenuate exposure–response relations.[37] When SYN-JEM was created, the crystalline silica exposure levels derived from the JEM were found to be of comparable magnitude to those observed in other studies.[22] SYN-JEM has previously confirmed known exposure–response relations for lung cancer.[38]

We found an increased risk of silicosis at cumulative exposure levels lower than in most existing studies. It is important to acknowledge that the cumulative exposure levels for the total study population are underestimated due to incomplete work histories. This limitation does, however, not affect the inception population. Additionally, SYN-JEM estimates geometric means rather than arithmetic means of exposure. Had we used arithmetic means, the cumulative exposure would have been approximately 60% higher. Low cumulative exposure levels in this nationwide population can also be attributed to individuals with relatively short duration of exposure, including short-term workers who are often excluded in industrial cohort studies. Nonetheless, the exposure levels within our cohort exhibit a good agreement with the above-mentioned industrial sand workers.[26] Finally, the use of a JEM to study diseases defined by an exposure, such as silicosis, may pose a problem, as cases of ILD are most likely to be labelled silicosis among the highest-exposed workers within an occupation, meaning that the JEM-assigned mean exposure estimates underestimate the actual exposure for diagnosed cases of silicosis. This problem does, however, not affect pulmonary sarcoidosis and idiopathic interstitial pneumonias.

Unexpectedly, we observed a number of silicosis cases in the non-exposed group. One reason for this finding may be cases who have worked in silica-exposed occupations prior to the first available register information on occupation in 1976. Furthermore, as a diagnosis of silicosis usually requires that the patient recalls previous silica exposure, there is a risk of ILD subtype misclassification if other dusts are mistaken for silica. Finally, rare silica-exposed work tasks within an otherwise unexposed occupation may not be captured in the JEM, which is a general limitation of JEM-based exposure estimation.

Using available register information, we adjusted for medications, connective tissue diseases and a proxy for radiation therapy, which are all associated with ILD risk. We adjusted for smoking, which is a risk factor for some types of ILD,[39] using a JEM which has performed well in previous studies.[40] This means that estimates of smoking, similarly to estimates of silica exposure, are tightly connected with occupation, and therefore, adjustment for smoking may entail a risk of bias towards the null. However, risk patterns were largely unchanged when the smoking covariate was excluded from analyses. Furthermore, in an analysis of blue-collar workers expected to be more homogenous in terms of lifestyle factors, we found risk patterns largely similar to those of the total study population, providing support that residual confounding by lifestyle factors has not significantly affected our results. We did not adjust for other occupational dust exposures associated with increased risk of ILD. Exposure to other dusts may potentially occur in most jobs assigned exposure to crystalline silica in SYN-JEM, for instance, to asbestos in construction or organic dust in agriculture,[21 41] and the lack of adjustment for these coexposures may have affected our results.

CONCLUSION

In conclusion, our findings suggest that silica inhalation may be related to pulmonary sarcoidosis and idiopathic interstitial pneumonias. These findings may, however, to some extent be explained by diagnostic misclassification of silicosis. We observed exposure–response relations for silicosis at lower cumulative exposure levels than previously reported, but these findings need to be corroborated in analyses that address the limitations of this study.

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Contributors IBI and HAK conceived and designed the study. JO, SP and HK developed the SYN-JEM ISCO-88 version. IBI and JMV established the dataset for analysis. IBI analysed the data and drafted the manuscript. All authors have contributed to interpreting the results, reviewed the paper for important intellectual content, approved the final version of the manuscript and take responsibility for the integrity of the work as a whole. IBI and HAK are guarantors of the study.

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