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Sarcoidosis and silica dust exposure among males in Sweden – a case-control study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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The study was approved by the Swedish Ethical Review Authority; DNR 2017/252.

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Abstract

Objective: To determine whether occupational exposure to silica dust causes an increased risk of developing sarcoidosis.

Design: Case-control study of all individuals between 20 and 65 years of age diagnosed with sarcoidosis (D86) in Sweden between 2005 and 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population. Information about occupation ad time of employment were collected from the Swedish Occupational Register.

Participants: All men and women aged 20-65 years old who were diagnosed sarcoidosis (D86) from 2007 to 2016 were included and assigned two controls, resulting 58136 cases and 116272 controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing sarcoidosis in men.

Results: The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation seems to be stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39). For males older than 35 with exposure to silica the prevalence of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of more than 10 years.

Conclusions: Occupational exposure to silica dust seems to increase the risk of sarcoidosis among males between 20 and 65 years of age. The risk seems to be higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Strengths and limitations of this study

- This case-control study includes all, in the included age groups, who were diagnosed with sarcidosis in Sweden from 2007 to the end of 2016.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area and therefore one could assume the distribution of these confounders among the cases and controls.

Key words: sarcoidosis, silica dust, case control study,

Background

Sarcoidosis is a systemic inflammatory disease that is characterised by the formation of granulomas in various organs, most commonly the lungs and/or intrathoracic lymph nodes. There are three diagnostic criteria for sarcoidosis: clinical and radiological presentation, non-caseating granulomas in biopsy tissue from the affected organ and ruling out alternative diagnoses [1]. In Sweden, the incidence is 11.5 per 100,000 per year with a peak in males aged 30–50 and in females aged 50–60. The incidence is heterogeneously spread across different counties. The proportion of males with sarcoidosis is slightly higher compared to females (56% versus 44%) [2].

The aetiology remains an unsolved problem. Suggestions have been made that sarcoidosis is a reaction to a currently unidentified environmental factor in genetically predisposed individuals [1]. Proposed environmental and occupational risk factors are, as suggested by the ACCESS (A Case-Control Etiologic Study of Sarcoidosis) study, insecticides, agricultural employment and mouldy, musty environments typically associated with bioaerosol exposure. In the ACCESS study, no associations with silica were found [3]. Another study, by Deubelbeiss et al., found that agricultural production and metal-processing industries near the residential area were environmental factors positively associated with the frequency of sarcoidosis [4]. Quartz, or silica/silica dust, has also been proposed to be an environmental factor, although there are currently only a handful of published studies on silica and sarcoidosis.

In Sweden, about 85,000 workers are exposed to silica dust by their profession [5]. Silica exposure is mainly known to cause silicosis, a fibrotic and potentially fatal lung disease [6]. Yet silica is not only associated with silicosis; a large case-control study from the United States investigating occupational silica exposure and risk of various diseases found an association with lung cancer, chronic obstructive pulmonary disorder (COPD), pulmonary tuberculosis and Rheumatoid arthritis (RA) as well. No associations with sarcoidosis were found [7].

Two studies on workers in iron foundries and construction workers exposed to airborne silica, respectively, found an increased risk for sarcoidosis in exposed workers [8 9]. In Iceland, a study on workers exposed to diatomaceous earth and cristobalite (crystalline silica) reported an increased incidence of sarcoidosis compared to the incidence for the general population of Iceland, however this study only included eight cases of sarcoidosis [10]. Furthermore, there are also a few case reports where silica is said to have caused sarcoidosis. In one case, cat litter containing mainly silica was considered the cause, and in another case silica as an excipient in oral drugs was blamed. Even silicone implant placement is believed to have caused sarcoidosis in one subject [11-13].

The aim of this study is to investigate whether sarcoidosis is associated with occupational exposure to silica.

Material and method

A unique personal identification number is distributed to all Swedish residents. Sweden holds various nation-wide registers, and with the use of the unique personal identification number it is possible to link data from several different registers, which provides a unique opportunity to analyse the entire patient population of Sweden. Since healthcare is paid through taxes, all inhabitants have equal access to health care and hospital services. This makes Sweden a country well-suited for epidemiological studies.

All individuals between 20 and 65 years of age and diagnosed with sarcoidosis in Sweden *(classified as D86 under the ICD10 standards)* between the 1st of January 2005 through the 31st of December 2016 were collected from the National non-primary outpatient care register. This register is maintained and validated by the Swedish National Board of Health and Welfare (NBHW) and contains data on registered outpatients of healthcare facilities throughout Sweden since 2001. However, when investigating the annual cases of sarcoidosis there was an elevated number of cases in the first two years after the register was established (2005–2006). This might be as a result of individuals being registered in the newly established register during follow-up medical examinations in addition to new cases. As the date of the first diagnosis cannot be established for the patients registered in the follow-up medical examinations, cases from 2005–2006 were thus excluded (wash-out period).

For each case of sarcoidosis, two control individuals from the general population were assigned by Statistics Sweden (SCB). The controls were selected to match the cases by age, sex and the county of residence at diagnosis. The controls must not themselves have sarcoidosis or be a first grade relative (sibling, parent or child) to the case. In addition, the controls were selected as to not have the following diagnoses: ankylosing spondylitis (M45), rheumatoid arthritis with rheumatoid factor (M05), other rheumatoid arthritis (MO6), Chron's disease (K50) or ulcerative colitis (K51).

To determine the occupation and time of employment in the cohort, the Swedish Occupational Register held and maintained by SCB was used. To be counted as quartz-exposed, the individual must have worked within a profession with exposure within the last five years. Cases or controls exposed to quartz earlier in life but not within the past five years or the study were excluded. The exposure for silica was estimated using a job-exposure matrix (JEM), PARCC-JEM, which is a generic and time-specific JEM including two time periods: 1975–1984 and 1985–1994 [14 15]. This JEM was developed by combining exposure measurements from Sweden, or when not available, other Nordic countries. The JEM was based on already existing information from a Swedish JEM developed for the Nordic Occupational Cancer Study, as well as an Airway Irritant-JEM, and thus gives apart from exposed occupations also provides information on exposure prevalence and exposure levels for each exposed job-title [14]. Jobs among the cases and controls that were, according to the JEM, classified as containing exposure to silica included concrete workers, casters, masons, ceramic and glass manufacturers, miners, etc.

The background characteristics are presented using descriptive statistics and are reported as number (n), percentage (%), mean and ± standard deviation. The odds ratio of being exposed to quartz in cases compared to controls was calculated using conditional logistic regression and are presented with 95% confidence intervals (CI). Stratification according to age in years (>35/≤35), sex

(male/female), cumulative exposure as mg/m^3 (0, 0.01–0.99, 1.0+), mean exposure as mg/m^3 (0, 0.01–0.05, 0.051+) and length of exposure in years (0–1, 2–5, 6–10, 11+) were made.

The study was approved by the Regional Ethical Committee in Uppsala; DNR 2017/252.

Results

From the National non-primary outpatient care register 6,740 cases of sarcoidosis in the ages between 20 to 65 years were collected. Each case was assigned two controls as described above (Figure 1). However, when using the JEM to evaluate silica exposure, the number of females exposed to silica was low (48 cases and 81 controls). The following results presented in this study were consequently only based upon data from the male cases and controls.

Included in the study were thus 3,663 cases and 7,329 controls, all male. The mean age of cases and controls was 44.7 years old (±10.9 SD). Of cases, 13.9% were exposed to quartz within the latest five years, of controls the proportion was 11.3%. Among cases there were 107 (2.9%) deaths whilst there were 128 (1.7%) among controls; the mean age at death event was 54.82 years of age in cases and 58.70 years of age in controls. In cases exposed to silica the mean age at death event was 50.73 years of age. The background characteristics are presented in Table 1.

Table 1: *Background characteristics*

	Cases	Controls
Males N (%)	3,663 (100%)	7,326 (100%)
Age at inclusion, mean (±SD)	44.7 (±10.9)	44.7 (±10.9)
Unexposed N (%)	3,154 (86.1%)	6,496 (88.7%)
Exposed N (%)	509 (13.9%)	830 (11.3%)
Years exposed to silica, mean (±SD)	7.50 (±4.8)	7.82 (±4.9)
Deaths, total N (%)	107 (2.9%)	128 (1.7%)
Deaths, unexposed N (%)	96 (2.6%)	117 (1.6%)
Deaths, exposed N (%)	11 (0.3%)	11 (0.2%)
Age at death event, total, mean (±SD)	54.82 (±11.46)	58.70 (±9.32)
Age at death event, unexposed, mean (±SD)	55.29 (±11.02)	58.78 (±9.33)
Age at death event, exposed, mean (±SD)	50.73 (±14.75)	57.82 (±9.6)

Overall, males with sarcoidosis were more likely to have been exposed to silica in their occupation within the previous five years (OR 1.27, 95% CI 1.13–1.43), as seen in Table 2. The association seems to be stronger in males diagnosed before 35 years of age (OR 1.48, 95% CI 1.16–1.87), but in males older than 35 years at diagnosis the association is also significant (OR 1.21, 95% CI 1.05–1.39). Since the confidence intervals overlap, it is not possible to tell if there really exists any difference depending on age at diagnosis.

Table 2: *Prevalence of sarcoidosis in males exposed to silica within five years of diagnosis stratified into length of exposure and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
All men				
Unexposed	3,154	6,496	1	
Exposed	509	830	**1.27**	**1.13–1.43**
Number of years with exposure:				
0 years	3,154	6,496	1	
1 year	110	200	1.13	0.90–1.44
2–5 years	142	221	**1.33**	**1.07–1.65**
6–10 years	188	304	**1.29**	**1.02–1.55**
>10 years	69	105	1.36	0.99–1.86
Age at diagnosis ≤35 years				
Unexposed	700	1,477	1	
Exposed	136	195	**1.48**	**1.1–1.87**
Number of years with exposure:				
0 years	700	1,477	1	
1 year	46	62	**1.59**	**1.07–2.35**
2–5 years	48	60	**1.70**	**1.16–2.51**
>5 years	42	73	1.21	0.82–1.78
Age at diagnosis >35 years				
Unexposed	2,454	5,019	1	
Exposed	373	635	**1.21**	**1.05–1.39**
Number of years with exposure:				
0 years	2,454	5,019	1	
1 year	64	138	0.94	0.70–1.28
2–5 years	94	161	1.19	0.92–1.55
6–10 years	149	241	**1.28**	**1.03–1.59**
>10 years	66	95	**1.44**	**1.04–2.00**

Number of years with exposure seems to matter. In all males with sarcoidosis, it was significantly more likely to have been exposed to silica for 2–10 years before diagnosis, than it was to not have been exposed at all. For men exposed to silica for more than 10 years there was also an increased risk for sarcoidosis, however not statistically significant.

When males were divided into age at diagnosis, the younger population with sarcoidosis (35 years or younger) was more likely to have been exposed to silica for a year or more, while the older population with sarcoidosis (older than 35 years) was more likely to have an exposed to silica for six or more years.

When the JEM was used to estimate the exposure frequency and exposure level to silica, not only was the length of exposure was found to be significant, but also the cumulative and mean exposure seems to be of importance (Table 3).

Table 3: *Prevalence of sarcoidosis in males exposed to silica within five years of diagnosis stratified into cumulative and mean exposure (mg/m^3) and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
Cumulative exposure				
Total men				
0	3,154	6,496	1	
0.01–0.99	461	752	**1.27**	**1.12–1.44**
≥1.0	48	78	1.06	0.67–1.68
Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.99	126	181	**1.47**	**1.15–1.89**
≥1.0	10	14	1.49	0.66–3.36
Age at diagnosis >35 years				
0	2,454	5,019	1	
0.01–0.99	335	571	**1.20**	**1.04–1.39**
≥1.0	38	64	1.22	0.81–1.83
Mean exposure				
Total Men				
0	3,154	6,496	1	
0.01–0.05	330	519	**1.32**	**1.14–1.52**
>0.05	179	311	1.19	0.98–1.44

Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.05	87	123	**1.50**	**1.12–2.00**
>0.05	49	72	1.44	0.99–2.10
Age at diagnosis >35 years				
0	2,454	5,019	1	
0.01–0.05	243	396	**1.26**	**1.07–1.49**
>0.05	130	239	1.12	0.90–1.39

Discussion

The aim of this longitudinal case-control study of the Swedish population was to examine whether cases with sarcoidosis have been exposed to silica at the workplace during the years 2007–2016 more often than controls. The prevalence of sarcoidosis in Sweden found in this study was 12 per 100,000. This is in agreement with a previous study that found a prevalence of sarcoidosis in Sweden of 11.5 per 100,000 [2]. However, the current study only investigated the age groups between 20–65 years of age.

Silica exposure seems to result in an increased risk for developing sarcoidosis in males. For females the prevalence of silica exposure was low (only 48 cases and 81 controls), and they where thus not included in this study (Figure 1). The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation seems to be stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39) (Table 2). However, the difference between the age groups were not statistically significant.

For the younger males (≤35 years) exposure to silica resulted in an increased risk of sarcoidosis, especially at shorter exposure time. Sarcoidosis can be subdivide into an acute form, Lövgren´s syndrome, and a more chronic form; the acute form culminates at age 25–30 [16]. This may explain why younger individuals have a shorter exposure time to onset of disease than do older individuals. For males older than 35 with exposure to silica the risk of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of m ore than 10 years (Table 2). When applying information about silica exposure levels from the JEM, both cumulative and mean exposure to silica where found to increase the risk of sarcoidosis (Table 3).

The increased risk for sarcoidosis among silica exposed young men (<35 years) is in line with observations from other studies which indicate that males seem to develop sarcoidosis at an earlier age than women, probably due to an environmental factor [2]. This suggested external factor could thus be occupational exposure to silica.

Agricultural employment has been considered a risk factor of developing sarcoidosis [3 4]. A study of farm workers in eastern North Carolina found that among particular agricultural activities the levels of respirable silica was above the limit [17]. Perhaps the reason why agricultural workers have an increased incidence of sarcoidosis is in fact that they are exposed to high amounts of silica in the soil.

A potential causative mechanism of sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance [18]. As noted above, our results suggest that inhaled silica dust may be such a causative or contributing exogenous factor. The mechanisms for how silica works as an exogenous factor is not known, but it has been shown that presence of silica in the lungs can drive macrophage polarisation towards type 2 macrophages [19]. Type 2 macrophages are suggested to be of importance for the formation of granulomas [20 21]. Silica exposure has also been shown to increase the risk for tuberculosis [22]; the explanation for this could also be the increased pool of M2 macrophages driven by silica exposure [19 20]. As suggested by Agrawal et al., perhaps sarcoidosis and tuberculosis are opposite ends of the same disease [23], but with silicosis driving the formation of granulomas.

Apart from silicosis, silica has also been associated with various systemic autoimmune diseases including RA, but also with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis [8 24 25]. This could also be attributed to M2 polarisation after silica exposure, as M2 macrophages might be a driver of the autoimmunity [26].

The main strength of this study is that all registered cases of sarcoidosis in Sweden between 2007–2016 were included by using a national, well maintained and validated register, and that not only sarcoid cases from specific occupations were included, as in previous studies [8 9]. The study's main weakness is the use of a JEM as an exposure matrix. The presence of silica dust at a job site does not in itself mean that all employees would have been exposed to the particles, thus this definition may have exaggerated the number of exposed individuals. However, the JEM has been developed independently of this study and if the JEM overestimated the detrimental level of silica exposure in the non-exposed cases, this would only weaken the correlation between exposure and morbidity. Another limitation of this study is that as this is a register study there is a lack in information on potential confounders. However, since the sample was large and the cases and controls were matched, it is reasonable to assume that the incidence of cofounding factors in the two groups is similar.

In Sweden, individuals who are exposed to silica at work undergo medical controls on a regular basis. These controls include X-rays and spirometry. Therefore, it is easy to believe that the increased risk of previously having worked with silica in cases with sarcoidosis could be due to asymptomatic cases being detected and diagnosed based on X-rays of the medical control. However, individuals employed at workplaces where silica exposure occurs undergo an X-ray before they become employees, which is why it can be concluded that changes in lung X-ray or symptoms from the lungs can only have occurred after exposure to silica began.

Conclusion

Exposure to silica increases the risk of sarcoidosis among males between 20 and 65 years of age. The risk seems to be higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Author contribution

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and JL, PV, ILB and PG interpreted the results. JL, LF, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

The data used in this study was derived from The Swedish National Patient Register, which is collected, maintained and owned by the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se). Access to data on the incidence of cardiovascular diseases in our cohort was granted based on the ethical committee's approval of undertaking this study. Any researcher, granted that they have an ethical approval from a regional ethical board, can use the data in the Swedish National Patient Register. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information. Data access requests can be directed to the Regional Ethical Board in Uppsala: https://www.epn.se/start/ or registrator@uppsala.epn.se.

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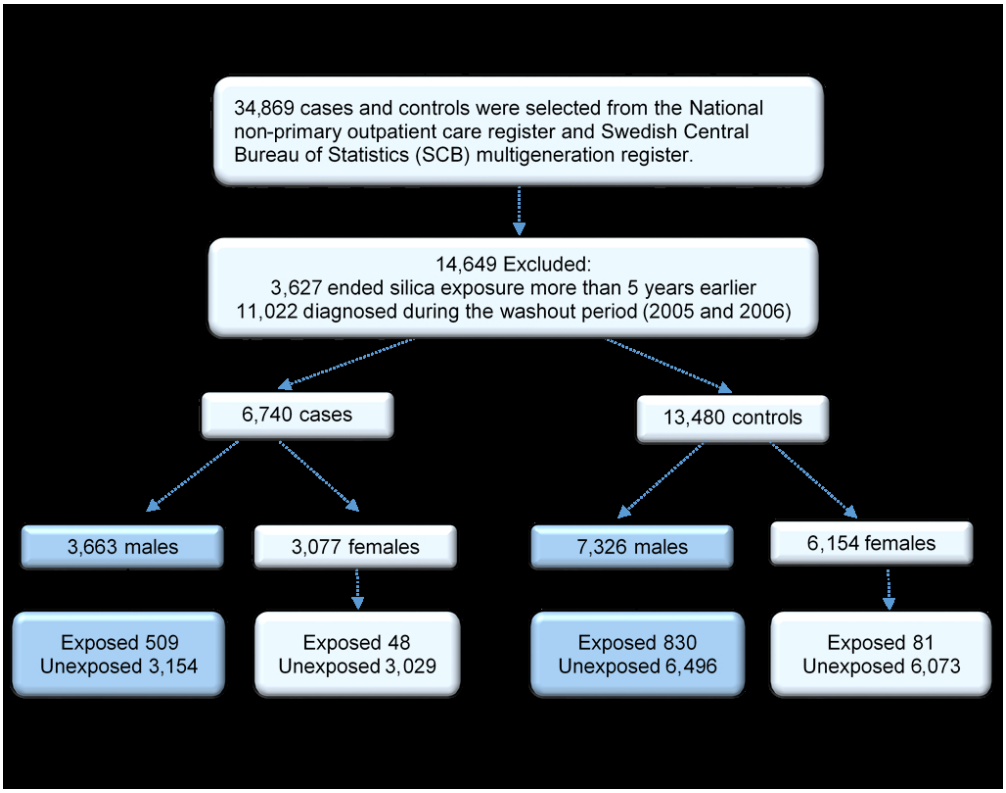
Figure legends

Figure 1 *Flowchart that visualises inclusion and exclusion of the study population.*



Flowchart that visualises inclusion and exclusion of the study population.

173x135mm (150 x 150 DPI)

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	5-6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
Statistical methods	#12c	Explain how missing data were addressed	5-6
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	5-6
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	7 and figure 1
Participants	#13b	Give reasons for non-participation at each stage	7 and

			figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	7 and table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	7
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	na
Main results	#16b	Report category boundaries when continuous variables were categorized	table 2 and 3
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7 and 9

Discussion

Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

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Sarcoidosis and silica dust exposure among males in Sweden – a case-control study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The Corresponding Author has the right to on behalf of all authors and does grant on behalf of all authors.

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The study was approved by the Swedish Ethical Review Authority; DNR 2017/252.

Word count: 2500

Abstract

Objective: To determine whether occupational exposure to silica dust is associated with an increased risk of developing sarcoidosis.

Design: Case-control study of all individuals between 20 and 65 years of age diagnosed with sarcoidosis (D86) in Sweden between 2007 and 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population. Information about occupation ad time of employment were collected from the Swedish Occupational Register.

Participants: All men and women aged 20-65 years old who were diagnosed sarcoidosis (D86) from 2007 to 2016 were included and assigned two controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing sarcoidosis in men.

Results: The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation seems to be stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39). For males older than 35 with exposure to silica the prevalence of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of more than 10 years.

Conclusions: Occupational exposure to silica dust seems to increase the risk of sarcoidosis among males between 20 and 65 years of age. The risk is higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Strengths and limitations of this study

- This case-control study includes all, in the included age groups, who were diagnosed with sarcidosis in Sweden from 2007 to the end of 2016.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area in order to reduce the impact of possible confounders.

Key words: sarcoidosis, silica dust, case control study,

Background

Sarcoidosis is a systemic inflammatory disease that is characterised by the formation of granulomas in various organs, most commonly the lungs and/or intrathoracic lymph nodes. There are three diagnostic criteria for sarcoidosis: clinical and radiological presentation, non-caseating granulomas in biopsy tissue from the affected organ and ruling out alternative diagnoses [1]. In Sweden, the incidence is 11.5 per 100,000 per year with a peak in males aged 30–50 and in females aged 50–60. The incidence is heterogeneously spread across different counties. The proportion of males with sarcoidosis is slightly higher compared to females (56% versus 44%) [2].

The aetiology remains an unsolved problem. Suggestions have been made that sarcoidosis is a reaction to a currently unidentified environmental factor in genetically predisposed individuals [1]. Proposed environmental and occupational risk factors are, as suggested by the ACCESS (A Case-Control Etiologic Study of Sarcoidosis) study, insecticides, agricultural employment and mouldy, musty environments typically associated with bioaerosol exposure. In the ACCESS study, no associations with silica were found [3]. Another study, by Deubelbeiss et al., found that agricultural production and metal-processing industries near the residential area were environmental factors positively associated with the frequency of sarcoidosis [4]. Respirable crystalline silica/ respirable silica dust, has also been proposed to be an environmental factor, although there are currently only a handful of published studies on silica and sarcoidosis.

In Sweden, about 85,000 workers are exposed to respirable silica dust by their profession [5]. Silica exposure is mainly known to cause silicosis, a fibrotic and potentially fatal lung disease [6]. Yet silica is not only associated with silicosis; a large case-control study from the United States investigating occupational silica exposure and risk of various diseases found an association with lung cancer, chronic obstructive pulmonary disorder (COPD), pulmonary tuberculosis and Rheumatoid arthritis (RA) as well. No associations with sarcoidosis were found [7].

Two studies on workers in iron foundries and construction workers exposed to airborne silica, respectively, found an increased risk for sarcoidosis in exposed workers [8 9]. In Iceland, a study on workers exposed to diatomaceous earth and cristobalite (crystalline silica) reported an increased incidence of sarcoidosis compared to the incidence for the general population of Iceland, however this study only included eight cases of sarcoidosis [10]. Furthermore, there are also a few case reports where silica is said to have caused sarcoidosis. In one case, cat litter containing mainly silica was considered the cause, and in another case silica as an excipient in oral drugs was blamed. Even silicone implant placement is believed to have caused sarcoidosis in one subject [11-13]. However, another case report argues that some cases of sarcoidosis might be misclassifications of silicosis [14].

The aim of this study is to investigate whether sarcoidosis is associated with occupational exposure to respirable silica dust.

Material and method

A unique personal identification number is distributed to all Swedish residents. Sweden holds various nation-wide registers, and with the use of the unique personal identification number it is possible to link data from several different registers, which provides a unique opportunity to analyse the entire patient population of Sweden. Since healthcare is paid through taxes, all inhabitants have equal access to health care and hospital services. This makes Sweden a country well-suited for epidemiological studies.

All individuals between 20 and 65 years of age and diagnosed with sarcoidosis in Sweden *(classified as D86 under the ICD10 standards)* between the 1st of January 2005 through the 31st of December 2016 were collected from the National non-primary outpatient care register. This register is maintained and validated by the Swedish National Board of Health and Welfare (NBHW) and contains data on registered outpatients of healthcare facilities throughout Sweden since 2001. However, when investigating the annual cases of sarcoidosis there was an elevated number of cases in the first two years after the register was established (2005–2006). This might be as a result of individuals being registered in the newly established register during follow-up medical examinations in addition to new cases. As the date of the first diagnosis cannot be established for the patients registered in the follow-up medical examinations, cases from 2005–2006 were thus excluded (wash-out period).

For each case of sarcoidosis, two control individuals from the general population were assigned by Statistics Sweden (SCB). The controls were selected to match the cases by age, sex and the county of residence at diagnosis. The controls must not themselves have sarcoidosis or be a first grade relative (sibling, parent or child) to the case. In addition, the controls were selected as to not have the following diagnoses: ankylosing spondylitis (M45), rheumatoid arthritis with rheumatoid factor (M05), other rheumatoid arthritis (MO6), Crohn's disease (K50) or ulcerative colitis (K51). These other diagnosis was excluded as this cohort is part of a larger cohort used in other studies [15 16].

To determine the occupation and time of employment in the cohort, the Swedish Occupational Register held and maintained by SCB was used. To be counted as silica-exposed, the individual must have worked within a profession with exposure to respirable silica dust within the last five years. Cases exposed to respirable silica dust earlier in life but not within the past five years before diagnosis were thus excluded together with their matched controls due to the gap between end of exposure and onset of disease. The exposure for respirable silica dust was estimated using an updated job-exposure matrix (JEM) based on the PARCC-JEM [17 18]. The updated PARCC-JEM is a time-specific JEM compromising the time period 1955-2014 and stratified into six 10 years periods. For the last two years of this study (2015-2016) the exposure assessment was done using the exposure data from the last 10 year period in the JEM. This JEM was developed by combining exposure measurements from Sweden, or when not available, other Nordic countries. The JEM was based on already existing information from a Swedish JEM developed for the Nordic Occupational Cancer Study, as well as an Airway Irritant-JEM, and thus gives apart from exposed occupations also provides information on exposure prevalence and exposure levels for each exposed job-title [17]. The exposure levels where for each occupation were obtained by calculating the product of exposure prevalence and exposure level for the relevant time periods. The JEM classifies jobs as exposed when at least 5% of the workers in a job is exposed to an annual mean level of 0.02 mg/m³ respirable crystalline silica dust. Jobs that matched those criteria included concrete workers, casters,

masons, ceramic and glass manufacturers, miners, etc. The background characteristics are presented using descriptive statistics and are reported as number (n), percentage (%), mean and ± standard deviation. The odds ratio of being exposed to respirable silica dust in cases compared to controls was calculated using conditional logistic regression and are presented with 95% confidence intervals (CI). Stratification according to age in years (>35/≤35), sex (male/female), cumulative exposure as mg/m^3*year (0, 0.01–0.99, 1.0+), mean exposure as mg/m^3 (0, 0.01–0.05, 0.051+) and length of exposure in years (0–1, 2–5, 6–10, 11+) were made. Thirty-five years of age was chosen as a stratification for age as to split the two incidence peaks found in the younger and older age groups [2]. For mean exposure, the stratification was chosen as below or above 0.05 mg/m^3 (which is 50% of the current Swedish OEL). There where to few high exposed to justify further classes for higher exposures. For cumulative exposure a division of the exposure below or above 1.0 mg/m^3*year was chosen on the basis that this is similar to 10 years of exposure at the current Swedish OEL (0.1 mg/m^3).

The study was approved by the Regional Ethical Committee in Uppsala; DNR 2017/252.

Results

From the National non-primary outpatient care register 6,740 cases of sarcoidosis in the ages between 20 to 65 years were collected. Each case was assigned two controls as described above (Figure 1). However, when using the JEM to evaluate silica exposure, the number of females exposed to silica was low (48 cases and 81 controls). The following results presented in this study were consequently only based upon data from the male cases and controls.

Included in the study were thus 3,663 cases and 7,329 controls, all male. The mean age of cases and controls was 44.7 years old (±10.9 SD). Of cases, 13.9% were exposed to respirable silica dust within the latest five years, of controls the proportion was 11.3%. The background characteristics are presented in Table 1.

Table 1: *Background characteristics*

	Cases	Controls
Males N (%)	3,663 (100%)	7,326 (100%)
Age at inclusion, mean (±SD, min-max)	44.7 (±10.9, 20-65)	44.7 (±10.9, 20-65)
Unexposed N (%)	3,154 (86.1%)	6,496 (88.7%)
Exposed N (%)	509 (13.9%)	830 (11.3%)
Years exposed to silica, mean (±SD, min-max)	7. 82 (±4.8, 1-17)	7.50 (±4.9, 1-25)

Overall, males with sarcoidosis were more likely to have been exposed to respirable silica dust in their occupation within the previous five years (OR 1.27, 95% CI 1.13–1.43), as seen in Table 2. The association is statistically significantly stronger (p=0.02) in males diagnosed before 35 years of age (OR 1.48, 95% CI 1.16–1.87), than in males older than 35 years at the time of diagnosis (OR 1.21, 95% CI 1.05–1.39).

Table 2: *Prevalence of sarcoidosis in males exposed to respirable silica dust within five years of diagnosis stratified into length of exposure and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
All men				
Unexposed	3,154	6,496	1	
Exposed	509	830	**1.27**	**1.13–1.43**
Number of years with exposure:				

0 years	3,154	6,496	1	
0.01–1.99 years	110	200	1.13	0.90–1.44
2.00–5.99 years	142	221	**1.33**	**1.07–1.65**
6.00–10.99 years	188	304	**1.29**	**1.02–1.55**
≥11.0 years	69	105	1.36	0.99–1.86
Age at diagnosis ≤35 years				
Unexposed	700	1,477	1	
Exposed	136	195	**1.48**	**1.1–1.87**
Number of years with exposure:				
0 years	700	1,477	1	
0.01–1.99 years	46	62	**1.59**	**1.07–2.35**
2.00–5.99 years	48	60	**1.70**	**1.16–2.51**
≥6.0 years	42	73	1.21	0.82–1.78
Age at diagnosis >35 years				
Unexposed	2,454	5,019	1	
Exposed	373	635	**1.21**	**1.05–1.39**
Number of years with exposure:				
0 years	2,454	5,019	1	
0.01–1.99 years	64	138	0.94	0.70–1.28
2.00–5.99 years	94	161	1.19	0.92–1.55
6.00–10.99 years	149	241	**1.28**	**1.03–1.59**
≥11.0 years	66	95	**1.44**	**1.04–2.00**

Number of years with exposure seems to matter. In all males with sarcoidosis, it was significantly more likely to have been exposed to silica for 2–10 years before diagnosis, than it was to not have been exposed at all. For men exposed to silica for more than 11 years there was also an increased risk for sarcoidosis, however not statistically significant.

When males were divided into age at diagnosis, the younger population with sarcoidosis (35 years or younger) was more likely to have been exposed to silica for a year or more, while the older population with sarcoidosis (older than 35 years) was more likely to have an exposed to silica for six or more years.

When the JEM was used to estimate the exposure frequency and exposure levels, exposure to respirable silica dust statistically significantly increase the OR for sarcoidosis, but neither the cumulative nor mean exposure show a statistical significant dose-response association (Table 3).

Table 3: *Prevalence of sarcoidosis in males exposed to respirable silica dust within five years of diagnosis stratified into cumulative (mg/m³*years) and mean (mg/m³) exposure and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
Cumulative exposure				
Total men				
0	3,154	6,496	1	
0.01–0.99	461	752	**1.27**	**1.12–1.44**
≥1.0	48	78	1.27	0.88–1.83
Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.99	126	181	**1.47**	**1.15–1.89**
≥1.0	10	14	1.49	0.66–3.36
Age at diagnosis >35 years				
0	2,454	5,019	1	
0.01–0.99	335	571	**1.20**	**1.04–1.39**
≥1.0	38	64	1.22	0.81–1.83
Mean exposure				
Total Men				
0	3,154	6,496	1	
0.01–0.05	330	519	**1.32**	**1.14–1.52**
>0.05	179	311	1.19	0.98–1.44
Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.05	87	123	**1.50**	**1.12–2.00**
>0.05	49	72	1.44	0.99–2.10
Age at diagnosis >35 years				
0	2,454	5,019	1	

0.01–0.05	243	396	**1.26**	**1.07–1.49**
>0.05	130	239	1.12	0.90–1.39

Discussion

The aim of this longitudinal case-control study of the Swedish population was to examine whether cases with sarcoidosis have been exposed to respirable silica dust at the workplace during the years 2007–2016 more often than controls. The incidence of sarcoidosis in Sweden found in this study was 12 per 100,000. This is in agreement with a previous study that found an incidence of sarcoidosis in Sweden of 11.5 per 100,000 [2]. However, the current study only investigated the age groups between 20–65 years of age.

Exposure to respirable silica dust seems to result in an increased risk for developing sarcoidosis in males. For females the prevalence of silica exposure was low (only 48 cases and 81 controls), and they where thus not included in this study (Figure 1). The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation was statistically significant stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39) (p=0.02) (Table 2).

For the younger males (≤35 years) exposure to respirable silica dust resulted in an increased risk of sarcoidosis, especially at shorter exposure time. Sarcoidosis can be subdivide into an acute form, Löfgren´s syndrome, which in Scandinavia can account for up 30 % of the sarcoidosis cases , and a more chronic form; the acute form culminates at age 25–30 [19-21]. This may explain why younger individuals have a shorter exposure time to onset of disease than do older individuals. There are some reports in the literature that silicosis can be misdiagnosed as sarcoidosis particularly in young men [14]. However, as sarcoidosis in Sweden are diagnosed using bronchoscopy, biopsy or bronchoalveolar lavage (BAL) the risk for misdiagnosis is small. Also Silicosis is currently rare in Sweden due to the fact that the legislation against silica and silica dust exposure have successfully reduced the occupational exposure levels [22]. For males older than 35 with exposure to silica the risk of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of more than 10 years (Table 2). When applying information about respirable silica dust exposure from the JEM, neither stratified cumulative nor mean exposure showed a statistical significant dose-response association (Table 3). There are, however, few high exposed individuals among the study population (Supplement 1). A previous study on respirable silica exposure and sarcoidosis in iron foundry workers found highest incidence rates among the individuals with the highest mean exposure [8].

The increased risk for sarcoidosis among young men (<35 years) exposed to respirable silica dust is in line with observations from other studies which indicate that males seem to develop sarcoidosis at an earlier age than women, probably due to an environmental factor [2]. This suggested external factor could thus be occupational exposure to silica. A potential causative mechanism of sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance [23]. As noted above, our results suggest that inhaled silica dust may be such a causative or contributing exogenous factor. The mechanisms for how silica works as an exogenous factor is not known, but it has been shown that presence of silica in the lungs can drive macrophage polarisation towards type 2 macrophages [24]. Type 2 macrophages are suggested to be of importance for the formation of granulomas [25 26]. Silica exposure has also been shown to increase the risk for tuberculosis [27]; the explanation for this could also be the increased pool of M2 macrophages driven

by silica exposure [24 25]. As suggested by Agrawal et al., perhaps sarcoidosis and tuberculosis are opposite ends of the same disease [28], but with silica driving the formation of granulomas.

Apart from silicosis, silica has also been associated with various systemic autoimmune diseases including RA, but also with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis [8 29 30]. This could also be attributed to M2 polarisation after silica exposure, as M2 macrophages might be a driver of the autoimmunity [31].

The main strength of this study is that all registered cases of sarcoidosis in Sweden between 2007–2016 were included by using a national, well maintained and validated register, and that not only sarcoid cases from specific occupations were included, as in previous studies [8 9]. The study's main weakness is the use of a JEM as an exposure matrix. The presence of respirable silica dust at a job site does not in itself mean that all employees would have been exposed. The JEM we have used tries to take this into account by estimating fraction of exposed within each job category, however it cannot be ruled out that this may have exaggerated the number of exposed individuals. However, the JEM has been developed independently of this study and if the JEM overestimated the detrimental level of silica exposure for non-exposed cases in the exposed occupations, this would only weaken the correlation between exposure and morbidity. Another limitation of this study is that as this is a register study there is a lack in information on potential confounders, such as smoking habits. In addition, other aspects which could influence the course of the disease, such as therapy, are not part of the register. However, cases and controls are matched based on age, sex and geographical area in order to reduce the impact of possible confounders.

In Sweden is mandatory to undergo medical controls on a regular basis that include lung x-ray and spirometry when your exposure to respirable silica dust is above 0.05 mg/m^3. Chest x-ray is conducted at start of work and then on regular basis (after 9 year and then every 6th year). It is therefore a risk for detecting asymptomatic cases of sarcoidosis among the exposed and the extra chest x-ray is a potential confounder. However, the increase in sarcoidosis is higher in low exposed group that are not enquired to undergo medical controls with chest x-ray. Also, workers with asymptomatic sarcoidosis would probably be predominantly identified at the first chest x-ray rather than later, and in this study the highest OR are found among the individuals with longer exposure times (Table 2).

Conclusion

Exposure to respirable silica dust increases the risk of sarcoidosis among males between 20 and 65 years of age. The risk seems to be higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Author contribution

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and JL, PV, ILB and PG interpreted the results. JL, PW, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

The data used in this study was derived from The Swedish National Patient Register, which is collected, maintained and owned by the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se). Access to data on the incidence of cardiovascular diseases in our cohort was granted based on the ethical committee's approval of undertaking this study. Any researcher, granted that they have an ethical approval from a regional ethical board, can use the data in the Swedish National Patient Register. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information. Data access requests can be directed to the Regional Ethical Board in Uppsala: https://www.epn.se/start/ or registrator@uppsala.epn.se.

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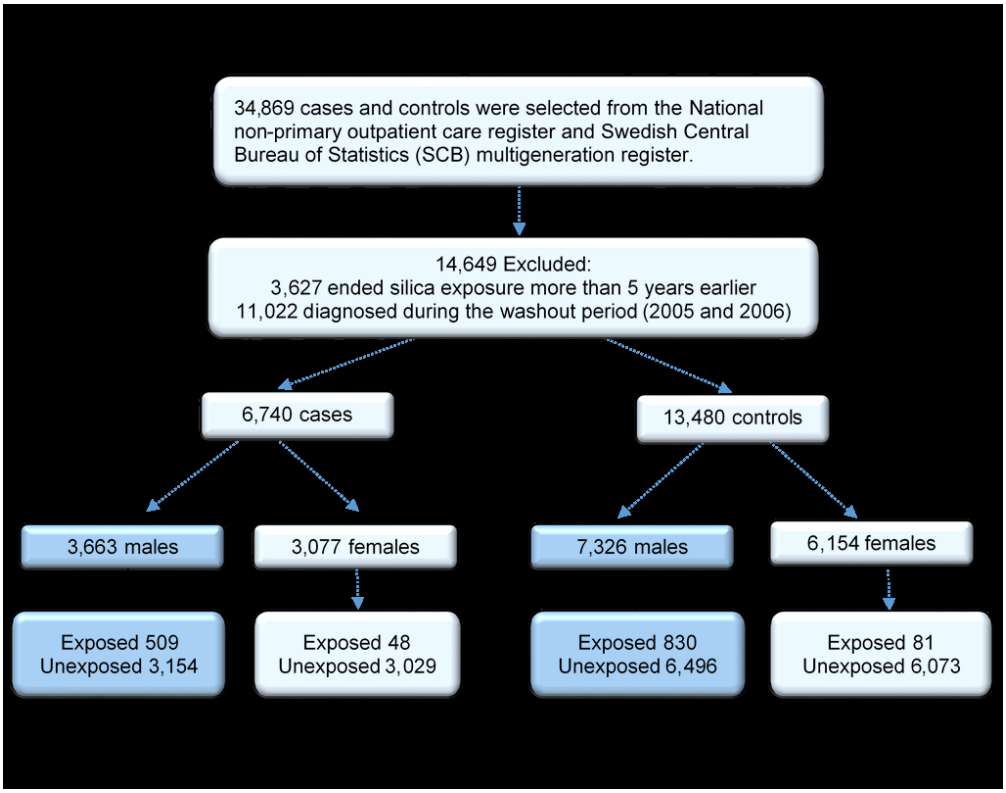
Figure legends

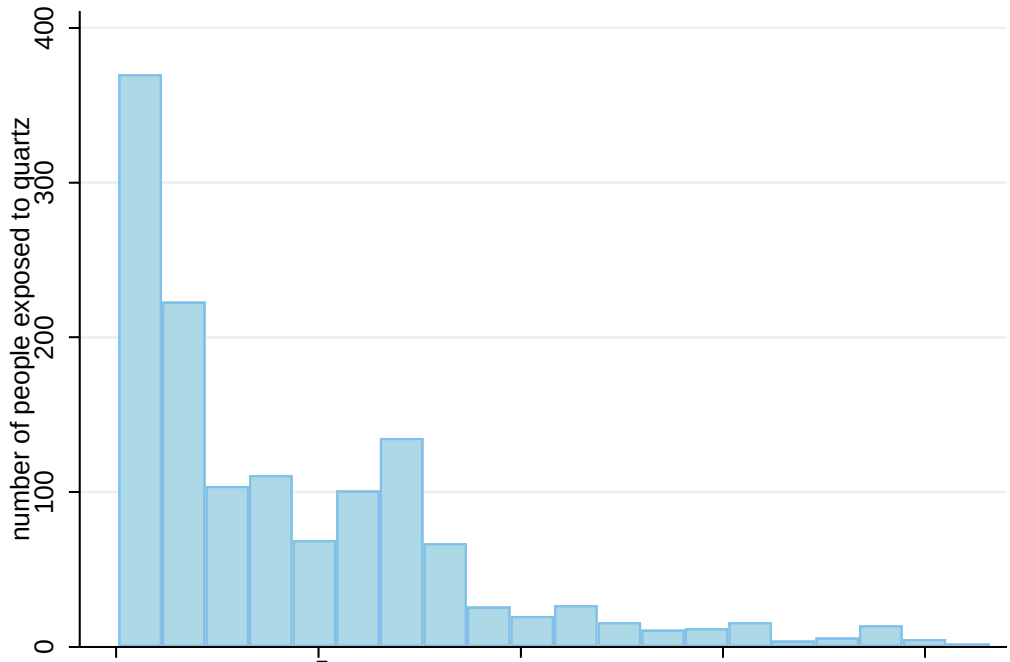
Figure 1 *Flowchart that visualises inclusion and exclusion of the study population.*

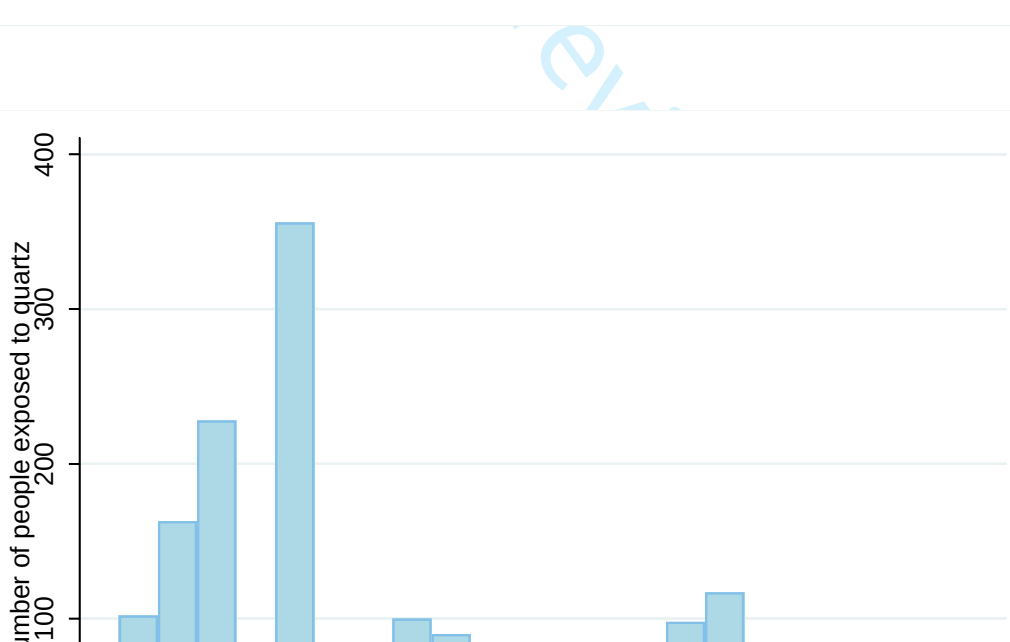


Flowchart that visualises inclusion and exclusion of the study population.

173x135mm (150 x 150 DPI)

Supplement 1: Distribution of cumulative and mean exposure estimates in the study population.





Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	5-6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
Statistical methods	#12c	Explain how missing data were addressed	5-6
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	5-6
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	7 and figure 1
Participants	#13b	Give reasons for non-participation at each stage	7 and

			figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	7 and table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	7
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	na
Main results	#16b	Report category boundaries when continuous variables were categorized	table 2 and 3
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7 and 9

Discussion

Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

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Sarcoidosis and silica dust exposure among males in Sweden – a case-control study

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Sarcoidosis and silica dust exposure among males in Sweden – a case-control study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The Corresponding Author has the right to on behalf of all authors and does grant on behalf of all authors.

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The study was approved by the Swedish Ethical Review Authority; DNR 2017/252.

Word count: 2500

Abstract

Objective: To determine whether occupational exposure to silica dust is associated with an increased risk of developing sarcoidosis.

Design: Case-control study of all individuals between 20 and 65 years of age diagnosed with sarcoidosis (D86) in Sweden between 2007 and 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population. Information about occupation ad time of employment were collected from the Swedish Occupational Register.

Participants: All men and women aged 20-65 years old who were diagnosed sarcoidosis (D86) from 2007 to 2016 were included and assigned two controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing sarcoidosis in men.

Results: The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation seems to be stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39). For males older than 35 with exposure to silica the prevalence of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of more than 10 years.

Conclusions: Occupational exposure to silica dust seems to increase the risk of sarcoidosis among males between 20 and 65 years of age. The risk is higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Strengths and limitations of this study

- This case-control study includes all, in the included age groups, who were diagnosed with sarcoidosis in Sweden from 2007 to the end of 2016.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area in order to reduce the impact of possible confounders.

Key words: sarcoidosis, silica dust, case control study,

Background

Sarcoidosis is a systemic inflammatory disease that is characterised by the formation of granulomas in various organs, most commonly the lungs and/or intrathoracic lymph nodes. There are three diagnostic criteria for sarcoidosis: clinical and radiological presentation, non-caseating granulomas in biopsy tissue from the affected organ and ruling out alternative diagnoses [1]. In Sweden, the incidence is 11.5 per 100,000 per year with a peak in males aged 30–50 and in females aged 50–60. The incidence is heterogeneously spread across different counties. The proportion of males with sarcoidosis is slightly higher compared to females (56% versus 44%) [2].

The aetiology remains an unsolved problem. Suggestions have been made that sarcoidosis is a reaction to a currently unidentified environmental factor in genetically predisposed individuals [1]. Proposed environmental and occupational risk factors are, as suggested by the ACCESS (A Case-Control Etiologic Study of Sarcoidosis) study, insecticides, agricultural employment and mouldy, musty environments typically associated with bioaerosol exposure. In the ACCESS study, no associations with silica were found [3]. Another study, by Deubelbeiss et al., found that agricultural production and metal-processing industries near the residential area were environmental factors positively associated with the frequency of sarcoidosis [4]. Respirable crystalline silica/ respirable silica dust, has also been proposed to be an environmental factor, although there are currently only a handful of published studies on silica and sarcoidosis.

In Sweden, about 85,000 workers are exposed to respirable silica dust by their profession [5]. Silica exposure is mainly known to cause silicosis, a fibrotic and potentially fatal lung disease [6]. Yet silica is not only associated with silicosis; a large case-control study from the United States investigating occupational silica exposure and risk of various diseases found an association with lung cancer, chronic obstructive pulmonary disorder (COPD), pulmonary tuberculosis and Rheumatoid arthritis (RA) as well. No associations with sarcoidosis were found [7].

Two studies on workers in iron foundries and construction workers exposed to airborne silica, respectively, found an increased risk for sarcoidosis in exposed workers [8 9]. In Iceland, a study on workers exposed to diatomaceous earth and cristobalite (crystalline silica) reported an increased incidence of sarcoidosis compared to the incidence for the general population of Iceland, however this study only included eight cases of sarcoidosis [10]. Furthermore, there are also a few case reports where silica is said to have caused sarcoidosis. In one case, cat litter containing mainly silica was considered the cause, and in another case silica as an excipient in oral drugs was blamed. Even silicone implant placement is believed to have caused sarcoidosis in one subject [11-13]. However, another case report argues that some cases of sarcoidosis might be misclassifications of silicosis [14].

The aim of this study is to investigate whether sarcoidosis is associated with occupational exposure to respirable silica dust.

Material and method

A unique personal identification number is distributed to all Swedish residents. Sweden holds various nation-wide registers, and with the use of the unique personal identification number it is possible to link data from several different registers, which provides a unique opportunity to analyse the entire patient population of Sweden. Since healthcare is paid through taxes, all inhabitants have equal access to health care and hospital services. This makes Sweden a country well-suited for epidemiological studies.

All individuals between 20 and 65 years of age and diagnosed with sarcoidosis in Sweden *(classified as D86 under the ICD10 standards)* between the 1st of January 2005 through the 31st of December 2016 were collected from the National non-primary outpatient care register. This register is maintained and validated by the Swedish National Board of Health and Welfare (NBHW) and contains data on registered outpatients of healthcare facilities throughout Sweden since 2001. However, when investigating the annual cases of sarcoidosis there was an elevated number of cases in the first two years after the register was established (2005–2006). This might be as a result of individuals being registered in the newly established register during follow-up medical examinations in addition to new cases. As the date of the first diagnosis cannot be established for the patients registered in the follow-up medical examinations, cases from 2005–2006 were thus excluded (wash-out period).

For each case of sarcoidosis, two control individuals from the general population were assigned by Statistics Sweden (SCB). The controls were selected to match the cases by age, sex and the county of residence at diagnosis. The controls must not themselves have sarcoidosis or be a first grade relative (sibling, parent or child) to the case. In addition, the controls were selected as to not have the following diagnoses: ankylosing spondylitis (M45), rheumatoid arthritis with rheumatoid factor (M05), other rheumatoid arthritis (MO6), Crohn's disease (K50) or ulcerative colitis (K51). These other diagnosis was excluded as this cohort is part of a larger cohort used in other studies [15 16].

To determine the occupation and time of employment in the cohort, the Swedish Occupational Register held and maintained by SCB was used. To be counted as silica-exposed, the individual must have worked within a profession with exposure to respirable silica dust within the last five years. Cases or controls exposed to respirable silica dust earlier in life but not within the past five years before diagnosis were thus excluded together with their matched controls/cases due to the gap between end of exposure and onset of disease. The exposure for respirable silica dust was estimated using an updated job-exposure matrix (JEM) based on the PARCC-JEM [17 18]. The updated PARCC-JEM is a time-specific JEM compromising the time period 1955-2014 and stratified into six 10 years periods. For the last two years of this study (2015-2016) the exposure assessment was done using the exposure data from the last 10 year period in the JEM. This JEM was developed by combining exposure measurements from Sweden, or when not available, other Nordic countries. The JEM was based on already existing information from a Swedish JEM developed for the Nordic Occupational Cancer Study, as well as an Airway Irritant-JEM, and thus gives apart from exposed occupations also provides information on exposure prevalence and exposure levels for each exposed job-title [17]. The exposure levels where for each occupation were obtained by calculating the product of exposure prevalence and exposure level for the relevant time periods. The JEM classifies jobs as exposed when at least 5% of the workers in a job is exposed to an annual mean level of 0.02 mg/m³ respirable crystalline silica dust. Jobs that matched those criteria included concrete workers, casters,

masons, ceramic and glass manufacturers, miners, etc. The background characteristics are presented using descriptive statistics and are reported as number (n), percentage (%), mean and ± standard deviation. The odds ratio of being exposed to respirable silica dust in cases compared to controls was calculated using conditional logistic regression and are presented with 95% confidence intervals (CI). Stratification according to age in years (>35/≤35), sex (male/female), cumulative exposure as mg/m^3*year (0, 0.01–0.99, 1.0+), mean exposure as mg/m^3 (0, 0.01–0.05, 0.051+) and length of exposure in years (0–1, 2–5, 6–10, 11+) were made. Thirty-five years of age was chosen as a stratification for age as to split the two incidence peaks found in the younger and older age groups [2]. For mean exposure, the stratification was chosen as below or above 0.05 mg/m^3 (which is 50% of the current Swedish OEL). There where to few high exposed to justify further classes for higher exposures. For cumulative exposure a division of the exposure below or above 1.0 mg/m^3*year was chosen on the basis that this is similar to 10 years of exposure at the current Swedish OEL (0.1 mg/m^3).

The study was approved by the Regional Ethical Committee in Uppsala; DNR 2017/252.

Results

From the National non-primary outpatient care register 11,623 cases of sarcoidosis in the ages between 20 to 65 years were collected. Each case was assigned two controls as described above giving in total 34,869 cases and controls (Figure 1). Of these 14,649 cases and controls where excluded: 11,796 due to the cases being diagnosed during the wash-our period and 2,853 due to either the case (480) or at least one of the controls (812) only having exposure to respirable silica dust that ended more than five years ago (i.e. they had been exposed to respirable silica dust earlier, but not within the past five years). In addition, when using the JEM to evaluate silica exposure, the number of females exposed to silica was low (48 cases and 81 controls). The following results presented in this study were consequently only based upon data from the male cases and controls.

Included in the study were thus 3,663 cases and 7,326 controls, all male. The mean age of cases and controls was 44.7 years old (±10.9 SD). Of cases, 13.9% were exposed to respirable silica dust within the latest five years, of controls the proportion was 11.3%. The background characteristics are presented in Table 1.

Table 1: *Background characteristics*

	Cases	Controls
Males N (%)	3,663 (100%)	7,326 (100%)
Age at inclusion, mean (±SD, min-max)	44.7 (±10.9, 20-65)	44.7 (±10.9, 20-65)
Unexposed N (%)	3,154 (86.1%)	6,496 (88.7%)
Exposed N (%)	509 (13.9%)	830 (11.3%)
Years exposed to silica, mean (±SD, min-max)	7. 82 (±4.8, 1-17)	7.50 (±4.9, 1-25)

Overall, males with sarcoidosis were more likely to have been exposed to respirable silica dust in their occupation within the previous five years (OR 1.27, 95% CI 1.13–1.43), as seen in Table 2. The association is statistically significantly stronger (p=0.02) in males diagnosed before 35 years of age (OR 1.48, 95% CI 1.16–1.87), than in males older than 35 years at the time of diagnosis (OR 1.21, 95% CI 1.05–1.39).

Table 2: *Prevalence of sarcoidosis in males exposed to respirable silica dust within five years of diagnosis stratified into length of exposure and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
All men				
Unexposed	3,154	6,496	1	

Exposed	509	830	**1.27**	**1.13–1.43**
Number of years with exposure:				
0 years	3,154	6,496	1	
0.01–1.99 years	110	200	1.13	0.90–1.44
2.00–5.99 years	142	221	**1.33**	**1.07–1.65**
6.00–10.99 years	188	304	**1.29**	**1.02–1.55**
≥11.0 years	69	105	1.36	0.99–1.86
Age at diagnosis ≤35 years				
Unexposed	700	1,477	1	
Exposed	136	195	**1.48**	**1.1–1.87**
Number of years with exposure:				
0 years	700	1,477	1	
0.01–1.99 years	46	62	**1.59**	**1.07–2.35**
2.00–5.99 years	48	60	**1.70**	**1.16–2.51**
≥6.0 years	42	73	1.21	0.82–1.78
Age at diagnosis >35 years				
Unexposed	2,454	5,019	1	
Exposed	373	635	**1.21**	**1.05–1.39**
Number of years with exposure:				
0 years	2,454	5,019	1	
0.01–1.99 years	64	138	0.94	0.70–1.28
2.00–5.99 years	94	161	1.19	0.92–1.55
6.00–10.99 years	149	241	**1.28**	**1.03–1.59**
≥11.0 years	66	95	**1.44**	**1.04–2.00**

Number of years with exposure seems to matter. In all males with sarcoidosis, it was significantly more likely to have been exposed to silica for 2–10 years before diagnosis, than it was to not have been exposed at all. For men exposed to silica for more than 11 years there was also an increased risk for sarcoidosis, however not statistically significant.

When males were divided into age at diagnosis, the younger population with sarcoidosis (35 years or younger) was more likely to have been exposed to silica for a year or more, while the older population with sarcoidosis (older than 35 years) was more likely to have an exposed to silica for six or more years.

When the JEM was used to estimate the exposure frequency and exposure levels, exposure to respirable silica dust statistically significantly increase the OR for sarcoidosis, but neither the cumulative nor mean exposure show a statistical significant dose-response association (Table 3).

Table 3: *Prevalence of sarcoidosis in males exposed to respirable silica dust within five years of diagnosis stratified into cumulative (mg/m³*years) and mean (mg/m³) exposure and age of diagnosis. Bold numbers indicate statistical significance (p<0.05).*

	Cases N	Controls N	OR	CI 95%
Cumulative exposure				
Total men				
0	3,154	6,496	1	
0.01–0.99	461	752	**1.27**	**1.12–1.44**
≥1.0	48	78	1.27	0.88–1.83
Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.99	126	181	**1.47**	**1.15–1.89**
≥1.0	10	14	1.49	0.66–3.36
Age at diagnosis >35 years				
0	2,454	5,019	1	
0.01–0.99	335	571	**1.20**	**1.04–1.39**
≥1.0	38	64	1.22	0.81–1.83
Mean exposure				
Total Men				
0	3,154	6,496	1	
0.01–0.05	330	519	**1.32**	**1.14–1.52**
>0.05	179	311	1.19	0.98–1.44
Age at diagnosis ≤35 years				
0	700	1,477	1	
0.01–0.05	87	123	**1.50**	**1.12–2.00**
>0.05	49	72	1.44	0.99–2.10

Age at diagnosis >35 years				
0	2,454	5,019	1	
0.01–0.05	243	396	**1.26**	**1.07–1.49**
>0.05	130	239	1.12	0.90–1.39

Discussion

The aim of this longitudinal case-control study of the Swedish population was to examine whether cases with sarcoidosis have been exposed to respirable silica dust at the workplace during the years 2007–2016 more often than controls. The incidence of sarcoidosis in Sweden found in this study was 12 per 100,000. This is in agreement with a previous study that found an incidence of sarcoidosis in Sweden of 11.5 per 100,000 [2]. However, the current study only investigated the age groups between 20–65 years of age.

Exposure to respirable silica dust seems to result in an increased risk for developing sarcoidosis in males. For females the prevalence of silica exposure was low (only 48 cases and 81 controls), and they where thus not included in this study (Figure 1). The prevalence of silica exposure at work was statistically significantly higher among male cases than controls (OR 1.27, 95% CI 1.13–1.43). For males of an age of 35 years or younger the correlation was statistically significant stronger (OR 1.48, 95% CI 1.1–1.87) than in older males (OR 1.21, 95% CI 1.05–1.39) (p=0.02) (Table 2).

For the younger males (≤35 years) exposure to respirable silica dust resulted in an increased risk of sarcoidosis, especially at shorter exposure time. Sarcoidosis can be subdivide into an acute form, Löfgren´s syndrome, which in Scandinavia can account for up 30 % of the sarcoidosis cases , and a more chronic form; the acute form culminates at age 25–30 [19-21]. This may explain why younger individuals have a shorter exposure time to onset of disease than do older individuals. There are some reports in the literature that silicosis can be misdiagnosed as sarcoidosis particularly in young men [14]. However, as sarcoidosis in Sweden are diagnosed using bronchoscopy, biopsy or bronchoalveolar lavage (BAL) the risk for misdiagnosis is small. Also silicosis is currently rare in Sweden due to the fact that the legislation against respirable silica dust exposure have successfully reduced the occupational exposure levels [22]. For males older than 35 with exposure to respirable silica dust the risk of sarcoidosis increased with the exposure time, with an OR of 1.44 (95% CI 1.04–2.00) for exposure of more than 10 years (Table 2). When applying information about respirable silica dust exposure from the JEM, neither stratified cumulative nor mean exposure showed a statistical significant dose-response association (Table 3). There are, however, few high exposed individuals among the study population (Supplement 1). A previous study on respirable silica exposure and sarcoidosis in iron foundry workers found highest incidence rates among the individuals with the highest mean exposure [8].

The increased risk for sarcoidosis among young men (<35 years) exposed to respirable silica dust is in line with observations from other studies which indicate that males seem to develop sarcoidosis at an earlier age than women, probably due to an environmental factor [2]. This suggested external factor could thus be occupational exposure to silica. A potential causative mechanism of sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance [23]. As noted above, our results suggest that inhaled silica dust may be such a causative or contributing exogenous factor. The mechanisms for how silica works as an exogenous factor is not known, but it has been shown that presence of silica in the lungs can drive macrophage polarisation towards type 2 macrophages [24]. Type 2 macrophages are suggested to be of importance for the formation of granulomas [25 26]. Silica exposure has also been shown to increase the risk for tuberculosis [27]; the explanation for this could also be the increased pool of M2 macrophages driven

by silica exposure [24 25]. As suggested by Agrawal et al., perhaps sarcoidosis and tuberculosis are opposite ends of the same disease [28], but with silica driving the formation of granulomas.

Apart from silicosis, silica has also been associated with various systemic autoimmune diseases including RA, but also with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis [8 29 30]. This could also be attributed to M2 polarisation after silica exposure, as M2 macrophages might be a driver of the autoimmunity [31].

The main strength of this study is that all registered cases of sarcoidosis in Sweden between 2007–2016 were included by using a national, well maintained and validated register, and that not only sarcoid cases from specific occupations were included, as in previous studies [8 9]. The study's main weakness is the use of a JEM as an exposure matrix. The presence of respirable silica dust at a job site does not in itself mean that all employees would have been exposed. The JEM we have used tries to take this into account by estimating fraction of exposed within each job category, however it cannot be ruled out that this may have exaggerated the number of exposed individuals. However, the JEM has been developed independently of this study and if the JEM overestimated the detrimental level of silica exposure for non-exposed cases in the exposed occupations, this would only weaken the correlation between exposure and morbidity. Another limitation of this study is that as this is a register study there is a lack in information on potential confounders, such as smoking habits. In addition, other aspects which could influence the course of the disease, such as therapy, are not part of the register. However, cases and controls are matched based on age, sex and geographical area in order to reduce the impact of possible confounders. The JEM used in this study only gives information on respirable silica exposure, hence other occupational exposures that might be linked to either sarcoidosis or sarcoid like granulomatous lung diseases such as chronic beryllium disease have not been investigated.

In Sweden is mandatory to undergo medical controls on a regular basis that include lung x-ray and spirometry when your exposure to respirable silica dust is above 0.05 mg/m^3. Chest x-ray is conducted at start of work and then on regular basis (after 9 year and then every 6th year). It is therefore a risk for detecting asymptomatic cases of sarcoidosis among the exposed and the extra chest x-ray is a potential confounder. However, the increase in sarcoidosis is higher in low exposed group that are not enquired to undergo medical controls with chest x-ray. Also, workers with asymptomatic sarcoidosis would probably be predominantly identified at the first chest x-ray rather than later, and in this study the highest OR are found among the individuals with longer exposure times (Table 2).

Conclusion

Exposure to respirable silica dust increases the risk of sarcoidosis among males between 20 and 65 years of age. The risk seems to be higher among exposed males 35 years or younger and older men with longer exposure (>6 years).

Author contribution

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and JL, PV, ILB and PG interpreted the results. JL, PW, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

The data used in this study was derived from The Swedish National Patient Register, which is collected, maintained and owned by the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se). Access to data on the incidence of cardiovascular diseases in our cohort was granted based on the ethical committee's approval of undertaking this study. Any researcher, granted that they have an ethical approval from a regional ethical board, can use the data in the Swedish National Patient Register. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information. Data access requests can be directed to the Regional Ethical Board in Uppsala: https://www.epn.se/start/ or registrator@uppsala.epn.se.

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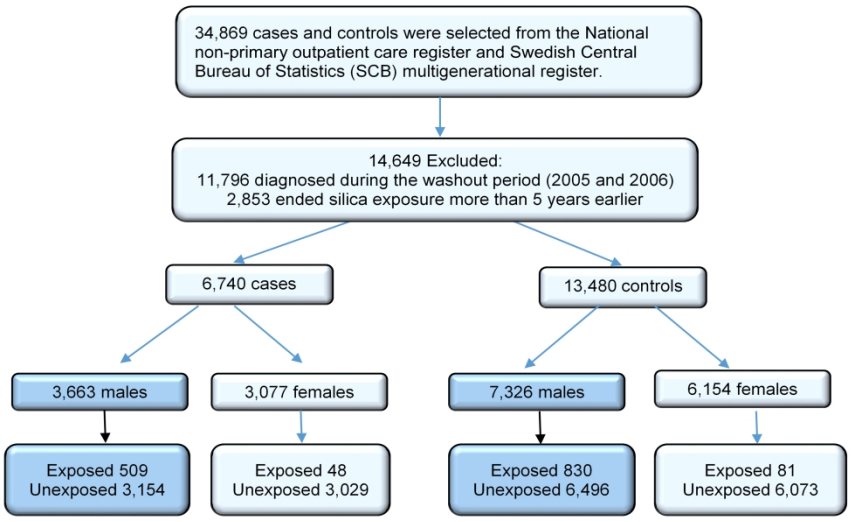
Figure legends

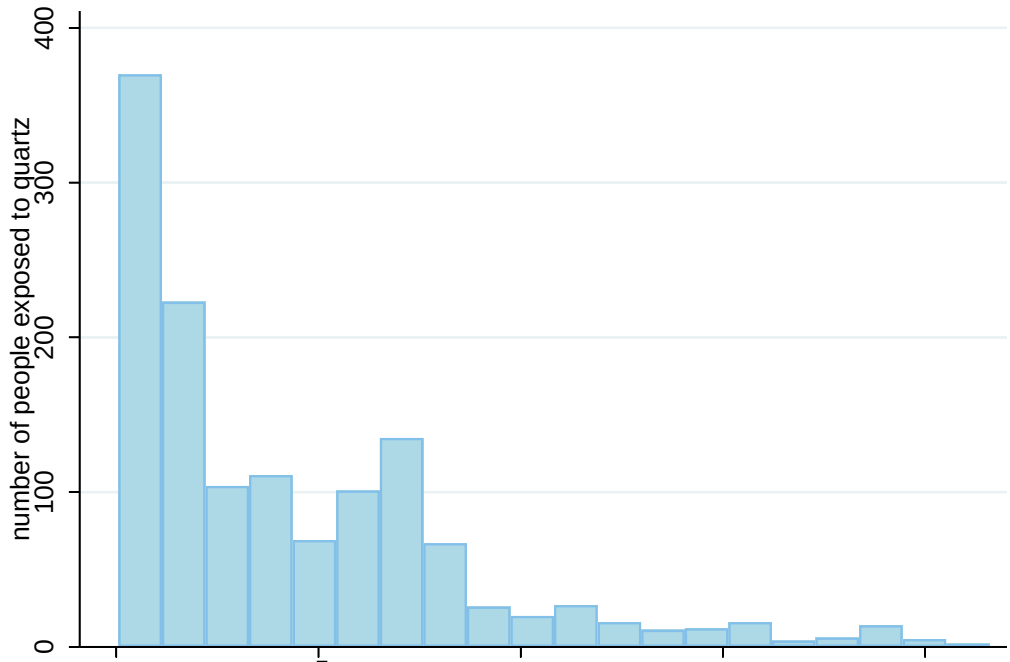
Figure 1 *Flowchart that visualises inclusion and exclusion of the study population.*

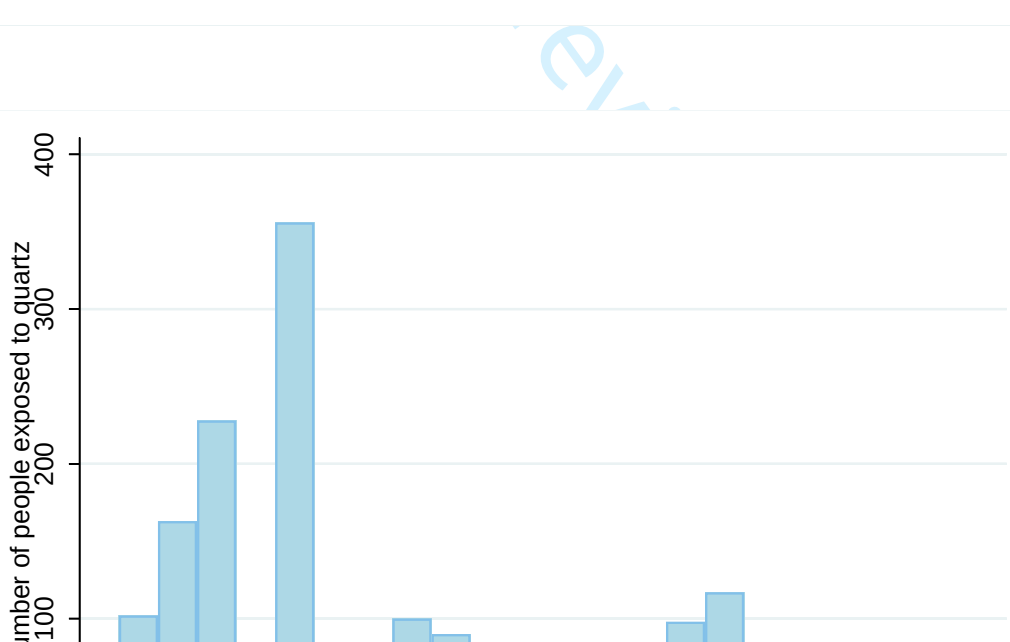


Flowchart that visualises inclusion and exclusion of the study population.

338x190mm (300 x 300 DPI)

Supplement 1: Distribution of cumulative and mean exposure estimates in the study population.





Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	5-6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
Statistical methods	#12c	Explain how missing data were addressed	5-6
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	5-6
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	7 and figure 1
Participants	#13b	Give reasons for non-participation at each stage	7 and

			figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	7 and table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	7
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	na
Main results	#16b	Report category boundaries when continuous variables were categorized	table 2 and 3
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7 and 9

Discussion

Key results	#18	Summarise key results with reference to study objectives	12
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12