

Silica Dust Exposure Increases Risk for Rheumatoid Arthritis

A Swedish National Registry Case–Control Study

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Objective: Rheumatoid arthritis (RA) is an inflammatory disease with unknown etiology. This study examines if silica dust exposure increases the risk for seropositive and seronegative RA. **Methods:** A nationwide registry case–control study was conducted that included all cases of RA in Sweden between 2005 and 2016. In total, 31,139 cases with two matched controls were included. A JEM was used to estimate exposure. **Results:** Silica dust exposure was associated with a statistically significant increase in odds ratio (OR) for seropositive (OR 1.22, 95% CI 1.05 to 1.40) and seronegative (OR 1.23, 95% CI 1.04 to 1.46) RA among men. **Conclusion:** This study found an increased OR for RA in silica-exposed men. The OR was equal for seropositive and seronegative RA. These findings further support the hypothesis that silica dust may be a trigger for RA.

Keywords: case–control study, occupational exposure, rheumatoid arthritis, silica

Rheumatoid arthritis (RA) is an inflammatory joint disease characterized by pain and swelling in the joints. RA is a chronic disease that can lead to decreased quality of life and, ultimately, joint destruction. It may also lead to premature death if not properly treated.¹ The disease affects somewhere between 0.5% and 1% of the population in the industrialized world.² Currently, the exact etiology remains

unknown. Previous studies have suggested a combination of genetic risks and possible environmental triggers. Certain known HLA shared epitope alleles, HLA-DRB1*01, and HLA-DRB1*4, are known to increase susceptibility for RA.^{3,4} Previous research points to smoking as an environmental trigger.^{4–6} The combined effects of the HLA-DRB1 alleles and smoking could initiate an immune response to anti-citrullinated peptide antibody (ACPA) and thereby lead to the development of seropositive RA.^{7,8} Infections of the respiratory system have also been linked to RA.^{9,10} These possible triggers point toward the lung being an initiating site of injury in ACPA-positive RA.¹¹ Occupational exposure to possibly inflammatory types of dust has also been linked to the development of RA. Textile dust, traffic pollution, and silica dust are all agents that have, in earlier research, been shown to increase the risk for ACPA-positive RA.^{12–14} These studies have not shown the same level of risk increase for ACPA-negative RA, suggesting either a difference in the pathogenesis or environmental triggers.

A recent meta-study on occupational exposure to silica found an association with an increased risk of developing RA.¹⁵ Professions with high silica exposure include foundry fitters, miners, and stonemasons. It is estimated that more than 3.2 million workers in the EU are exposed to silica dust in their professions.¹⁶ Inhaled silica dust has been linked to silicosis, sarcoidosis, and COPD.^{17–19} In certain cases, silica has also been suspected of causing lung cancer and is currently classed as a carcinogen by the IARC.²⁰ Silica dust exposure can also increase the risk of chronic kidney disease.²¹

There have been several articles investigating the role of silica dust and RA. One of the larger studies, containing 18,335 cases, found modest support for an association between crystalline silica exposure and rheumatoid arthritis.²² However, this study used death certificates to determine if cases had RA. A recent Danish register study also found an incidence rate ratio for RA among silica-exposed men.²³

This study aimed to examine if silica dust exposure increases the risk for RA and if there was a difference in risk for developing seropositive RA and seronegative RA.

METHODS AND MATERIALS

Swedish residents all have roughly equal access to healthcare services. Each person also has a unique personal identification number. The data was collected from the National non-primary outpatient care register kept by the Swedish National Board of Health and Welfare (NBHW). All patients between the age of 20 and 65 who had been diagnosed with M05 (seropositive Rheumatoid arthritis) or M06 (seronegative Rheumatoid arthritis) according to the International Classification of Diseases, 10th Edition (ICD-10), between 2005 and 2016 were included in the study. The seropositive RA (M05) cases in the register are generally conformed as ACPA positive. The information was then matched against the register for the cause of death, kept by the NBHW. This register is maintained and validated by NBHW and contains data on registered outpatients of healthcare facilities throughout Sweden. In total, 31,139 cases were initially included. However, when investigating the annual cases, there was an elevated number of cases in the first 2 years under investigation (2005 to 2006). This high number might be a result of individuals being registered in the newly established register during follow-up medical

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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, no important aspects of the study have been omitted; 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 authors report no conflicts of interest.

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

Clinical significance: The clinical significance of this paper is the finding that silica dust exposure is associated with a statistically significant increased risk for Rheumatoid Arthritis among silica-exposed men. Our findings suggest that the risk for seronegative and seropositive RA risk is equal. This underlines the possible health hazards regarding silica exposure.

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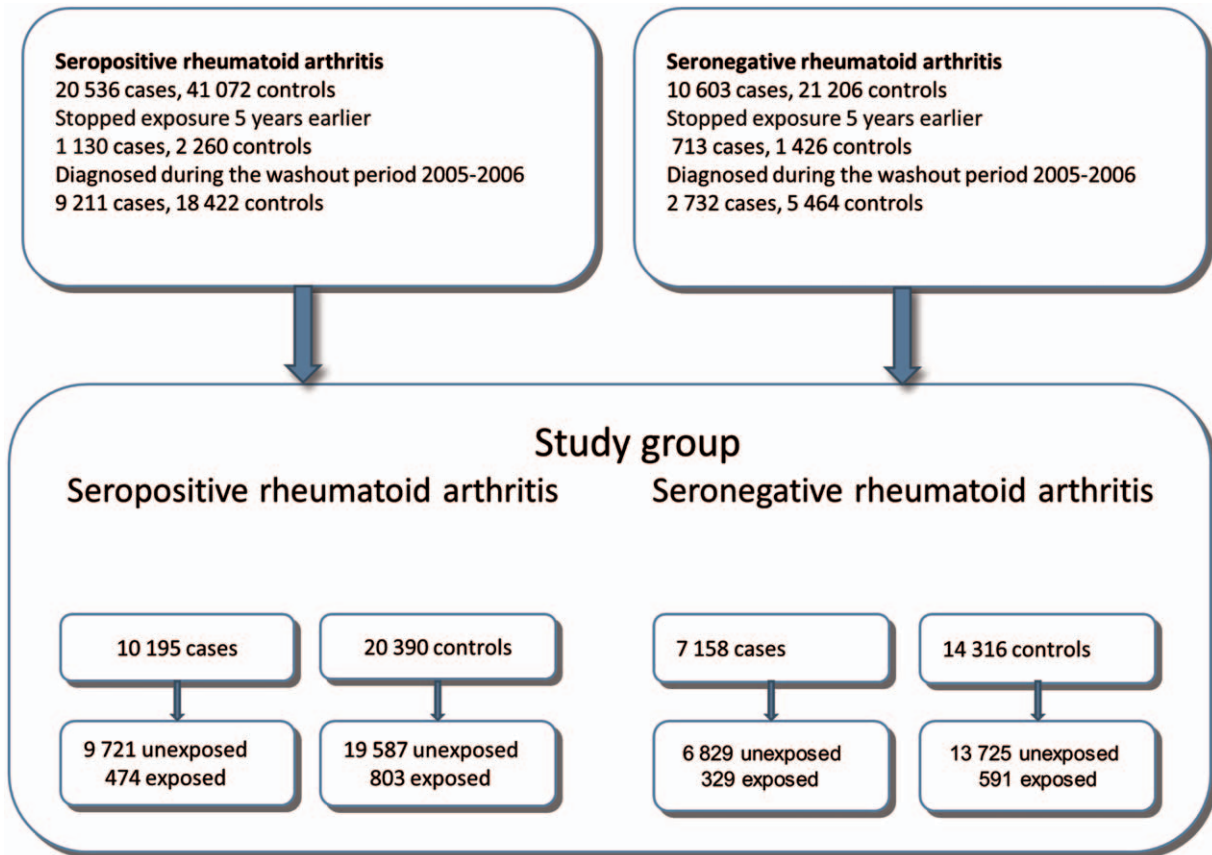


FIGURE 1. Flow chart of included and excluded cases.

examinations in addition to new cases. Because the first diagnosis date cannot be established for the patients registered in the follow-up medical examinations, cases from 2005 to 2006 were thus excluded (as a wash-out period), see Figure 1.

Two controls were included for each patient. The controls were not first-degree relatives of the case and did not have the diagnosis M06/M05. They were the same age and sex. They resided in the same county during the time that the patient received their diagnosis. The Swedish Central Bureau of Statistics (SCB) provided the controls using their multigenerational register, which contains information regarding biological and adopted first-degree relatives of all Swedish residents since 1961 of people born 1932 or later. The individuals included in the study were then checked in the SCBs longitudinal integrated database for health insurance and labor market studies (LISA) to see what occupation the individual had and for how long they worked in that profession and the register for emigration (SCB). Occupations with exposure to silica dust were then identified using a modified version of the Finnish Information System on Occupational Exposure job-exposure matrix (FINJEM).^{24,25}

Statistical Analysis

A CLR was used to analyze the results. Stata: Software for Statistics and Data Sciences for windows was used to run the CLR.

The data investigated all RA and were divided into seropositive and seronegative RA (M05/M06). A separate analysis was then run, sorting cases by their years of exposure stratified into less than 1 year of employment, 1 to 5 years of employment, and 5 to 10 years of employment and more than 10 years of employment. The relevant results are displayed in tables, and those results with lesser significance are mentioned in the text.

Ethical Considerations

The Regional Ethics Commission in Uppsala, Sweden approved the study (DNR 2017/252).

RESULTS

In total, 31,139 cases were included in the study. Of these cases, 20,536 were seropositive (M05) and 10,603 were seronegative (M05). Each case had two matched controls (Fig. 1).

A higher frequency of men had been exposed compared to women in both the case and control groups. This fact was also true for both seropositive RA and seronegative RA. RA was roughly three times more common among women than men in this study. Men were more likely to be employed in professions exposed to silica. Less than a fifth of all included subjects had at any time been exposed to silica dust at their workplace. The majority of those that had been exposed had only been exposed for 1 to 5 years. The mean age at inclusion was 52 years for men and 29 years for women. For seronegative RA, the mean age was 50 for men and 48 for women. The mean age for seropositive RA was 53 for men and 50 for women (Table 1).

Exposure to silica dust gave a statistically higher risk of being diagnosed with RA, odds ratio (OR) of 1.17 (CI 95% 1.07 to 1.28) (Table 2). The risk was highest among those people exposed for more than 10 years, OR of 1.33 (CI 95% 1.10 to 1.61), but an increased risk was also found with shorter exposure time. The same trend was found for men but not women (Table 2) when the study population was stratified according to sex.

Exposure to silica dust gave an increased risk for seropositive RA, OR of 1.20 (CI 95% 1.07 to 1.35) when the cases were stratified into seropositive or seronegative RA (Table 3). However,

TABLE 1. Descriptive Statistics of the Study Population

		Total		Seropositive Rheumatoid Arthritis		Seronegative Rheumatoid Arthritis	
		Cases	Controls	Cases	Controls	Cases	Controls
Number of participants (%)	Men	4482 (26)	8964 (26)	2523 (25)	5046 (25)	1959 (27)	3918 (27)
	Women	12,871 (74)	25,742 (74)	7672 (75)	15,344 (75)	5199 (73)	10,398 (73)
Age at inclusion (±SD)	Men	52 (11)	52 (11)	53 (11)	53 (11)	50 (12)	50 (12)
	Women	49 (12)	49 (12)	50 (12)	50 (12)	48 (12)	50 (12)
Number of exposed (%)	Men	589 (13)	987 (11)	340 (14)	572 (11)	249 (13)	415 (11)
	Women	214 (2)	407 (2)	134 (2)	231 (2)	80 (2)	176 (2)
Years with exposure (±SD)	Men	6.7 (4.2)	6.4 (4.3)	6.8 (4.2)	6.5 (4.1)	6.5 (4.4)	6.2 (4.4)
	Women	5.3 (3.7)	5.0 (3.8)	5.4 (3.7)	5.0 (3.6)	5.2 (3.8)	5.0 (4.1)
Diseased (%)	Men	246 (6)	293 (3)	170 (7)	186 (4)	76 (4)	107 (3)
	Women	366 (3)	445 (2)	250 (3)	273 (2)	116 (2)	172 (2)

no increased risk was found for seronegative RA for the total population.

For both seropositive and seronegative RA, the same trend was observed as for total RA (Table 3), were men who had more than 10 years of exposure had the highest risk with an OR of 1.33 (CI 95% 1.01 to 1.75) for seropositive RA and OR of 1.46 (CI 95% 1.04 to 2.03) for seronegative RA. No excess risk was observed for women.

DISCUSSION

Our results are mostly in line with previous research on the subject. Several studies have shown a link between APCA positive RA and silica dust.^{14,26} However, the current study, which comprises all registered cases of seropositive and seronegative RA,

found an increased OR for men of both seropositive and seronegative RA; OR for seropositive RA 1.22 (CI 95% 1.05 to 1.40) and OR for seronegative RA 1.23 (CI 95% 1.04 to 1.46) (Table 2).

The results indicate that silica-exposed men had a statistically significant risk for RA. When stratified into seropositive and seronegative RA, an increased risk for men was found for both. The risk was highest among those men with the longest exposure. No statistically significant risk was found for women. The reason why the risk increase was greater for men could be because of a difference in actual job exposure. For example, two people employed in the same profession could have widely different levels of exposure due to differences in the performance of tasks. One could speculate if men are more exposed than women within the same occupation.^{27,28}

TABLE 2. All Included Cases and Controls of Rheumatoid Arthritis (RA)

	Cases, N	Controls, N	OR	95% CI
Total				
Unexposed	16,550	33,312	1	
Exposed	803	1394	1.17	1.07–1.28
Number of years with exposure				
0 years	16,550	33,312	1	
≤1 years	136	286	0.96	0.78–1.18
1.01–5 years	213	353	1.22	1.03–1.46
5.01–10 years	266	467	1.16	0.99–1.35
>10 years	188	288	1.33	1.10–1.61
Men				
Unexposed	3893	589	1	
Exposed	7977	987	1.22	1.10–1.36
Number of years with exposure				
0 years	3893	7977	1	
≤1 years	95	184	1.05	0.82–1.35
1.01–5 years	136	220	1.27	1.02–1.58
5.01–10 years	205	355	1.18	0.99–1.41
>10 years	153	288	1.38	1.12–1.71
Women				
Unexposed	12,657	25,335	1	
Exposed	214	407	1.05	0.89–1.25
Number of years with exposure				
0 years	12,657	25,335	1	
≤1 years	41	102	0.81	0.56–1.16
1.01–5 years	77	133	1.16	0.87–1.54
5.01–10 years	61	112	1.09	0.80–1.50
>10 years	35	60	1.17	0.77–1.77

Bold numbers indicate statistical significance (*P* < 0.05).

The data are also shown for both men and women and grouped according to years of silica dust exposure. OR, odds ratio.

TABLE 3. All Included Cases and Controls Stratified Into Seropositive and Seronegative Rheumatoid Arthritis (RA) and Sorted by Sex and Years of Silica Dust Exposure

	Exposed to Quartz Within 5 yrs Before Diagnosis 2007–2016							
	Seropositive Rheumatoid Arthritis				Seronegative Rheumatoid Arthritis			
	Cases	Controls	OR	CI 95%	Cases	Controls	OR	CI 95%
Total								
Unexposed	9721	19,587	1		6829	13,725	1	
Exposed	474	803	1.20	1.07–1.35	329	591	1.13	0.98–1.30
Number of years with exposure								
0 years	9721	19,587	1		6829	13,725	1	
≤1 year	75	150	1.01	0.77–4.34	61	136	0.90	0.66–1.23
1.01–5 years	121	204	1.21	0.96–1.52	92	149	1.25	0.96–1.63
5.01–10 years	166	282	1.20	0.98–1.46	100	185	1.10	0.85–1.41
>10 years	112	167	1.37	1.07–1.76	76	121	1.27	0.95–1.71
Men								
Unexposed	2183	4474	1		1710	3503	1	
Exposed	340	572	1.22	1.05–1.40	249	415	1.23	1.04–1.46
Number of years with exposure								
0 years	2183	4474	1		1710	3503	1	
≤1 year	51	95	1.09	0.78–1.54	44	89	1.00	0.70–1.45
1.01–5 years	73	128	1.17	0.87–1.57	63	92	1.40	1.00–1.94
5.01–10 years	126	210	1.23	0.98–1.54	79	145	1.12	0.84–1.49
>10 years	90	139	1.33	1.01–1.75	63	89	1.46	1.04–2.03
Women								
Unexposed	7538	15,113	1		5119	10,222	1	
Exposed	134	231	1.16	0.94–1.44	80	176	0.91	0.69–1.19
Number of years with exposure								
0 years	7538	15,113	1		5119	10,222	1	
≤1 year	24	55	0.88	0.54–1.42	17	47	0.72	0.41–1.26
1.01–5 years	48	76	1.26	0.88–1.81	29	57	1.01	0.64–1.60
5.01–10 years	40	72	1.12	0.76–1.64	21	40	1.05	0.62–1.79
>10 years	22	28	1.57	0.90–2.75	13	32	0.81	0.43–1.54

Bold numbers indicate statistical significance ($P < 0.05$).
OR, odds ratio.

The findings in this study correlate well with what was found in a Danish study, where men exposed to silica at work had an increased incidence rate for RA, but not silica-exposed women.²³

Silica dust exposure has previously been found to increase the risk for RA, even for non-smokers for specifically ACPA-positive RA.^{26,29} It also seems that the combination of smoking and silica dust has a synergistic relationship in RA development. However, according to other studies, this situation seems to be true only for seropositive RA.⁶ The finding of an equal OR for seronegative and seropositive RA for silica-exposed men might indicate that the burden of smoking has been reduced in the general population. The results presented in the current study might predominantly be attributed to silica exposure. The results also correlate with a previous Swedish study where silica-exposed men showed an increased risk for both seronegative and seropositive RA.³⁰

This study may overestimate the total exposure since it only measured years of exposure. Consequently, the exposure of a stonemason with high levels of exposure is counted as equal to a glassblower with low levels of exposure. This approach might also underestimate the risk increase as well. The main strength of the study is the large number of cases included, which consist of all registered cases in Sweden for the time period of the study.

The main limitations of this study are that the estimations for exposure are based upon a JEM. There are no data on possible confounders, such as smoking⁴ in the register used. However, it is reasonable to assume that the prevalence of smoking is roughly the same in cases and controls. If there is a difference, it would most likely be that those people not exposed to silica dust are more likely

to be employed in better-paid jobs and a higher socioeconomic status. Because of these factors, they are less likely to smoke.³¹ Generally, jobs with high silica dust are labor intensive, associated with lower socioeconomic status. Still, the majority of lower-paying occupations do not have significant levels of silica dust exposure.

CONCLUSION

Silica dust exposure is associated with a statistically significant increase in risk for seropositive and seronegative RA among silica-exposed men. The same increased risk was not seen for women. The results are in line with previous studies regarding seropositive RA or total RA. However, the finding that the OR for seronegative and seropositive RA risk was equal differs from other studies which found that seropositive RA was predominant in occupational exposure. The findings in the current study further underlines the possible health hazards regarding occupational silica exposure.

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