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ORIGINAL ARTICLE

Occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study

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ABSTRACT

Objective Airborne agents including cigarette smoke associate with an increased risk of rheumatoid arthritis (RA). We analysed to which extent occupational exposure to asbestos and silica confers an increased risk of developing serologically defined subsets of RA.

Methods This Swedish population-based case-control study enrolled incident RA cases between 1996 and 2013 (n=11 285), identified through national public authority and quality registers, as well as from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) Study. Controls (n=1 15 249) were randomly selected from Sweden's population register and matched on sex, age, index year and county. Occupational histories were obtained from national censuses. Exposure to asbestos and silica was assessed by job-exposure matrices. Logistic regression was used to calculate ORs adjusted for age, sex, county, index year, alcohol use and smoking.

Results Results showed that male workers exposed to asbestos had higher risk of seropositive RA (OR=1.2, 95% CI 1.0 to 1.4) and seronegative RA (OR=1.2, 95% CI 1.0 to 1.5) compared with unexposed workers. The risk was highest among workers exposed to asbestos from 1970, before a national ban was introduced. Male workers exposed to silica also had higher risk of RA (seropositive RA: OR=1.4, 95% CI 1.2 to 1.6; seronegative RA: OR=1.3, 95% CI 1.0 to 1.5). For the largest subset, seropositive RA, the OR increased with the number of years exposed to silica, up to OR=2.3 (95% CI 1.4 to 3.8, p for trend <0.0001). Women overall had lower ORs than men, but the duration and intensity of their exposure were lower.

Conclusions In conclusion, we observed an association between asbestos exposure and risk of developing RA and extended previous findings of an association between silica exposure and RA risk, where a dose-response relationship was observed.

Key messages

What is already known about this subject?

- Exposure to silica is known to be associated with an increased risk of mainly seropositive RA, whereas the risk from exposure to asbestos is unknown.

What does this study add?

- Ever exposure to asbestos and silica are associated with an increased risk of both seropositive and seronegative RA among men.
- The risk of RA increases with years of exposure to asbestos and silica.

How might this impact on clinical practice?

- Workers exposed to combinations of silicate minerals and smoking have a particularly elevated risk of RA and constitute an important target group.
- The demonstrated association between exposure to asbestos and silica and risk of RA merits special attention in countries where exposure to these agents is still high.

INTRODUCTION

The lung has an important role in the development of rheumatoid arthritis (RA), as a site where immune reactions contributing to later RA may be initiated.[1] It has been suggested that airborne exposures such as cigarette smoke may participate in the initiation of immune reactions against antigens that are accumulated or formed in the lungs, and this hypothesis is supported by the fact that years of cigarette consumption increase the risk of RA.[2 3]

Further support for this aetiological hypothesis comes from the observations that occupations related to manufacturing, construction and production, which include airborne exposure to inorganic dusts, are associated with an increased risk of RA.[4–7] Exposure to one such agent, silica, has been shown to increase the risk of RA,[8–10] and interact with cigarette smoking in conferring an increased

risk for seropositive RA.[11] It is thus of interest to investigate if other airborne agents are also associated with an increased risk for RA.

One occupational agent of particular interest is asbestos, which is known to cause inflammation and increase the risk of fibrosis and cancer in the lungs.[12] However, the knowledge regarding any association between exposure to asbestos and RA is scarce.[4 5 13 14] Both asbestos and silica are naturally occurring silicon-containing compounds. Exposure to silica usually requires mechanical processing of quartz-containing bedrock or concrete, whereas exposure to asbestos occurs more easily when handling the material itself. Import and use of asbestos was forbidden in Sweden in 1982, but the material is still present in buildings constructed before the 1980s. Hence workers within the construction industry are still at risk of being exposed to asbestos, for example, during renovation of buildings.

The aim of this study was to estimate the influence of occupational exposure to the silicate minerals asbestos and silica on the risk of developing RA.

MATERIALS AND METHODS

In the present population-based case-control study we linked data on sociodemographic characteristics, medical care and death from national registers and other sources of data with the unique Swedish personal number. The study base consisted of adult residents from all parts of Sweden,≥18 years of age, between 1996 and 2013. Figure 1 shows the inclusion and exclusion of participants. The study population originally consisted of 13 444 RA cases and 139 972 controls.

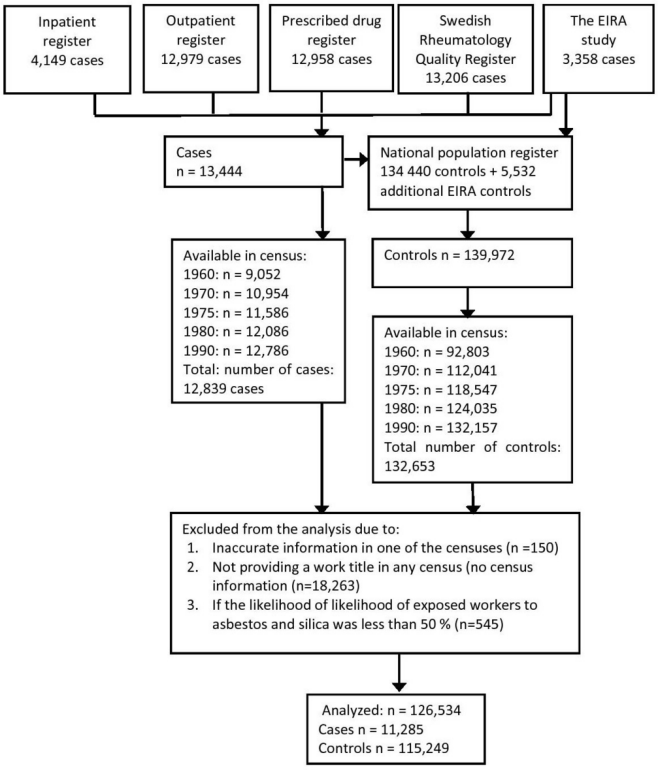

Figure 1 Flow chart of inclusion and exclusion of study participants. EIRA, Epidemiological Investigation of Rheumatoid Arthritis.

Identification of cases and controls

Patients with RA were identified from the Swedish EIRA Study (n=3358) and from three national registers; the National Patient Register (NPR) (n=13 036), the Swedish Rheumatology Quality Register (SRQ) (n=13 206) and the Swedish Prescribed Drug Register (SPDR) (n=12 958).

Cases identified through NPR, SRQ and SPDR were enrolled between 2006 and NPR, 2013. NPR contains information on inpatient visits and specialist outpatient care visits, and thereby included the first registered date of RA and information on RA diagnosis.[15] SRQ is a national clinical quality register which is used for follow-up of patients at rheumatology clinics as part of standard care.[16] SPDR included information about dispensed prescription drugs. We defined patients as incident RA cases if they fulfilled all four following criteria:

1. A first-time visit to the inpatient or specialist outpatient care in 2006 or later according to the NPR and with a main or contributory diagnosis of seropositive or seronegative RA, according to the International Statistical Classification of Diseases and Related Health Problems (ICD10) (M05: Rheumatoid arthritis with rheumatoid factor, M06: Other rheumatoid arthritis, M12.3: Palindromic rheumatism), or been enrolled as an incident patient with RA in SRQ in 2006 or later.
2. A second inpatient discharge or specialist outpatient care visit, with a main or contributory diagnosis of seropositive or seronegative RA, within 1 year of the first visit.
3. At least one of the above visits should have taken place at an internal medicine or rheumatology department.
4. Received disease-modifying antirheumatic drug treatment (registered for RA) with biologics, non-biologic treatment, gold, prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, according to the prescribed drug register.

The EIRA Study is a population-based case-control study. We included cases from EIRA enrolled from 1996 until 2013. To be defined as a case, patients had to be diagnosed with RA according to the American College of Rheumatology 1987 classification criteria.[17] All participants in the EIRA Study were asked to fill in an extensive questionnaire on environmental factors and to provide blood samples. The questionnaire is in Swedish and can be obtained from the corresponding author on request. The design of the EIRA Study has been described in detail elsewhere.[18 19]

For each case identified through NPR, SRQ, SPDR and EIRA 10 controls were randomly selected from the total population register and individually matched on age, county, sex and index year.[20] Index year was defined as the year prior to cases receiving their diagnosis among cases and matched controls. For each case in EIRA one to two additional controls were selected from the national

population register and these controls answered the same extensive questionnaire on environment and lifestyle as the EIRA cases.

Definition of main exposures

Sweden has a long tradition of regular enumerations of residents and housing since the mid-18th century. From 1960 until 1990, these censuses were coordinated in so-called Population and Housing Censuses, which were carried out every fifth year. Population and Housing Censuses collected data using questionnaires for the entire population in combination with data collected from various registers.

Occupational titles were available in the Population and Housing Censuses carried out in 1960, 1970, 1975, 1980 and 1990. Participants were excluded if work titles in all five censuses were missing or unknown. A job-exposure matrix (JEM) containing historical exposure estimates on asbestos and silica was applied to each study participant's occupational titles.[21–23] The JEM contained exposure estimates for the time periods 1955–1964, 1965–1972, 1973–1977, 1978–1984 and 1985–1995. For each occupation the intensity level and probability of exposure for asbestos and silica was defined. Asbestos exposure was defined as occupational, inhalable exposure to any form of asbestos or asbestos-containing material. Silica exposure was defined as occupational exposure to respirable (aerodynamic diameter <5 um) crystalline silica-containing dusts (eg, granite). Additional information about the JEM can be provided by PW.

We wanted to make sure that participants in the analysis had actually been exposed to asbestos and silica. Hence, we excluded participants with low probability to both exposures according to the JEM, as they would never be part of the main analysis (n=545). We further restricted the analysis to participants with at least one occupation with ≥50% probability of exposure to the main independent variable. Participants exposed to both asbestos and silica seldom had a work history with high probability of exposure to both of these silicate minerals, which made it difficult to study combinations of these two exposures in the same table. For transparency, we present a table with different combinations of exposure to asbestos and/or silica as a online supplementary table, including all exposed workers, independent of their probability of exposure to either silicate mineral.

Statistical analysis

We used unconditional logistic regression to assess the ORs and 95% CIs of overall RA, seropositive RA or seronegative RA associated with exposure to asbestos or silica as the main exposure. In each analysis asbestos and silica were analysed separately and only workers who had ever had an occupation with at least 50% likelihood of being exposed to the main exposure according to the JEM were considered exposed. We performed one test for trend in the logistic regression analysis by treating the number of occupations classified as exposed to asbestos or silica as a continuous variable. Values of $p<0.05$ were considered statistically significant.

All analyses were adjusted for the matching variables sex, county, age and index year. Age was measured in years and was treated as a continuous variable. County was a categorical variable with the 21 counties in Sweden. Index year was treated as a categorical variable in the analysis and divided into three categories. Smoking and alcohol consumption were considered potential confounders. Information on these confounders was collected for participants in the EIRA Study through a questionnaire. Smoking was assessed as pack-years. One pack-year was defined as 20 cigarettes smoked per day for 1 year. It was treated as a continuous variable with never smokers as the reference group. Alcohol was defined as high, moderate or no consumption versus low consumption of alcohol, based on drinks consumed per week prior to the index year. Asbestos and silica were adjusted for each other as ever exposure (categorised as unexposed, low probability or high probability of exposure). Analyses were restricted to men when the number of exposed women was low. Quadratic terms for the continuous variables age and smoking were added to the model to allow for non-linearity.

We used the EIRA Study information on smoking and alcohol consumption to impute values for missing data according to the fully conditional specification method[24] under the missing at random assumption. Our imputation model included the variables in the analysis model as well as seropositive status, birth year, whether participants had belonged to the EIRA Study or not, disposable household income during 1990, 2000 and 2010. Squared terms were added for the continuous variables. We generated 20 imputed data sets with the PROC MI and PROC MIANALYZE command in SAS V.9.4. We compared characteristics between participants with complete and incomplete data (see table 1).

RESULTS

Table 1 shows the distribution of sociodemographic and lifestyle related factors among the 11 285 cases and 115 249 controls included in the analyses. Among men, 17% of cases and 12% of controls were classified as having ever been occupationally exposed to asbestos and 19% of cases and 13% of controls as ever exposed to silica. Among women, less than 1% of cases or controls were categorised as exposed.

In table 2 we present overall results for ever exposure to asbestos or silica. Male workers exposed to asbestos had about 20% higher risk of both seropositive RA and seronegative RA than workers unexposed to asbestos after adjustment for age, sex, county, index year, smoking, alcohol consumption and silica. Female workers exposed to asbestos also appeared to have an increased risk of seropositive RA in the crude model, but the association decreased after adjustment for potential confounding from smoking, alcohol consumption and silica. Exposure

Table 1 Characteristics of participants in the analysis stratified by variables with complete or incomplete data (n=126 534)

	Seropositive RA			Seronegative RA			Controls		
	Observed	**Imputed**	**All**	**Observed**	**Imputed**	**All**	**Observed**	**Imputed**	**All**
Complete data	n=7887	n=0		n=3398	n=0		n=115 249	n=0	
Age (median)	59	–		62	–		60	–	
Women (%)	70	–		63	–		68	–	
Exposed to asbestos (%)	5	–		6	–		4	–	
Exposed to silica (%)	7	–		7	–		5	–	
Incomplete data									
Education	n=7876	n=11	n=7887	n=3391	n=7	n=3398	n=114 992	n=257	n=115 249
≤9 years (%)	31	55	31	30	36	30	27	36	27
10–12 years (%)	46	33	46	45	44	45	45	43	45
>12 years (%)	24	11	24	24	21	24	28	21	28
Smoking	n=2026	n=5861	n=7887	n=659	n=2739	n=3398	n=4356	n=110 893	n=115 249
Ever smoking (%)	72	70	70	57	57	57	55	57	56
Pack-years (median)	18	19	19	15	14	14	13	14	14
Alcohol consumption	n=2168	n=5719	n=7887	n=716	n=2682	n= 398	n=4700	n=110 549	n=115 249
Non-drinkers (%)	10	7	8	9	7	8	6	7	7
Low consumption (%)	54	54	54	51	51	51	47	46	46
Moderate consumption (%)	21	22	22	23	23	23	24	24	24
High consumption (%)	15	17	17	17	19	18	23	22	22

RA, rheumatoid arthritis;.

Table 2 OR of RA together with 95% CI among workers classified as ever exposed to asbestos or silica compared with workers classified as never exposed (n=1 26 534)

	All RA cases				Seropositive RA			Seronegative RA		
	Exposed cases/controls	Unexposed cases/controls	Median intensity for asbestos (fibre/cm^3) and silica (mg/m^3)	Median years since last occupation classified as exposed	Crude OR (95% CI)*	Adjusted OR (95% CI)†	Crude OR (95% CI)*	Adjusted OR (95% CI)†	Crude OR (95% CI)*	Adjusted OR (95% CI)†
Asbestos										
Men	603/4624	2151/24 033	0.10	35	1.5 (1.3 to 1.6)	1.2 (1.0 to 1.3)	1.6 (1.4 to 1.8)	1.2 (1.0 to 1.4)	1.4 (1.2 to 1.6)	1.2 (1.0 to 1.5)
Women	17/139	7359/75 526	0.02	32	1.3 (0.8 to 2.1)	1.0 (0.6 to 1.7)	1.5 (0.9 to 2.6)	1.1 (0.6 to 2.0)	–	–
Men and women‡	620/4763	9510/99 559	0.10	35	1.5 (1.3 to 1.6)	1.1 (1.0 to 1.2)	1.5 (1.4 to 1.7)	1.1 (0.9 to 1.2)	1.3 (1.1 to 1.6)	1.2 (1.0 to 1.4)
Silica										
Men	678/4703	2956/32 361	0.08	25	1.6 (1.4 to 1.7)	1.3 (1.2 to 1.5)	1.7 (1.5 to 1.9)	1.4 (1.2 to 1.6)	1.4 (1.2 to 1.6)	1.3 (1.0 to 1.5)
Women	64/532	7558/77 370	0.10	29	1.2 (0.9 to 1.6)	1.1 (0.8 to 1.5)	1.4 (1.1 to 1.9)	1.2 (0.8 to 1.7)	0.8 (0.4 to 1.4)	0.8 (0.4 to 1.5)
Men and women‡	742/5235	10 514/109 731	0.08	26	1.5 (1.4 to 1.7)	1.3 (1.2 to 1.5)	1.6 (1.5 to 1.8)	1.4 (1.2 to 1.5)	1.3 (1.1 to 1.5)	1.2 (1.0 to 1.4)

*Adjusted for county, age and index year.
†Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and silica were adjusted for each other.
‡ Additionally adjusted for sex.
RA, rheumatoid arthritis.

to silica was associated with an increased risk of both seropositive RA and seronegative RA among men, but not among women. The ORs among men for seropositive and seronegative RA was 1.4 (95% CI 1.2 to 1.6) and 1.3 (95% CI 1.0 to 1.5) after adjustment for potential confounding from smoking, alcohol consumption and asbestos exposure.

The ORs of RA among workers exposed to asbestos or silica in different censuses is shown in table 3. Few workers were exposed to asbestos from census 1980 and onwards. The highest OR was noted among male workers exposed from 1970, observed in both seropositive and seronegative RA, with an adjusted OR for overall RA of 1.3 (95% CI 1.1 to 1.5). For silica, the risk of seropositive RA appeared higher when exposure had occurred in earlier censuses, whereas the opposite tendency was observed for seronegative RA. The highest OR among both men and women for seropositive RA was found among workers exposed from 1960 (adjusted OR: 1.6, 95% CI 1.3 to 2.1 and 1.6, 95% CI 0.8 to 3.1 for men and women, respectively). For seronegative RA, the highest OR was observed among male workers exposed in the census of 1990 (OR=1.6, 95% CI 1.1 to 2.4).

In table 4, we present the ORs of RA among men according to number of occupations where exposure to asbestos or silica was reported. The risk of seropositive and seronegative RA appeared to be higher among men who had been exposed to asbestos in several censuses, based on the crude model. After adjustments for potential lifestyle-related confounders, there was no statistically significant risk estimate, but the tendency of an exposure-response relation between number of censuses exposed to asbestos and risk of seropositive or seronegative RA subtype remained. For seropositive RA, we observed a positive exposure-response trend (p=0.0075). Men who had been exposed to asbestos in all five censuses had an OR of 1.4 (95% CI 1.0 to 1.8) for overall RA compared with unexposed workers. Similarly, for silica exposure, the risk of both the seropositive and seronegative RA subtype appeared to increase with number of censuses being exposed. After adjustment for potential confounders, this association remained strong for seropositive RA, though we did observe a positive dose-response trend for both seropositive and seronegative RA. Men being exposed in three, four or five censuses had a significantly increased risk, where the highest risk was found among male workers who reported an exposed occupation in all five censuses (adjusted OR: 2.3, 95% CI 1.4 to 3.8).

We explored the risk of RA from different combinations of smoking and asbestos or silica exposure (table 5). The highest risk estimates were found among smoking workers for seropositive RA, regardless of whether these workers had been exposed to asbestos or not. The same was observed for silica. Male and female smokers exposed to silica had an OR of 4.1 (95% CI 2.7 to 6.4) and 2.7 (95% CI 1.0 to 6.9), respectively, for seropositive RA. As was noted for asbestos, female and male workers exposed

Table 3 OR of RA together with 95% CI among workers classified as ever exposed to asbestos or silica in different censuses compared with workers classified as never exposed (n=126 534)

	All RA cases					Seropositive RA		Seronegative RA	
	Cases/ controls	Median intensity for asbestos (fibre/ cm^3) and silica (mg/m^3)	Median years since last occupation classified as exposed	Crude OR (95% CI)*	Adjusted OR (95% CI)†	Crude OR (95% CI)*	Adjusted OR (95% CI)†	Crude OR (95% CI)*	Adjusted OR (95% CI)†
Asbestos									
Men									
Unexposed workers	2151/24 033			1.0	1.0	1.0	1.0	1.0	1.0
Exposed from 1960	84/781	0.10	40	1.2 (1.0 to 1.5)	1.0 (0.8 to 1.3)	1.2 (0.9 to 1.6)	1.0 (0.7 to 1.4)	1.2 (0.8 to 1.7)	1.1 (0.7 to 1.6)
Exposed from 1970	306/2148	0.11	35	1.7 (1.5 to 1.9)	1.3 (1.1 to 1.5)	1.7 (1.5 to 2.0)	1.3 (1.1 to 1.6)	1.5 (1.2 to 1.9)	1.3 (1.0 to 1.7)
Exposed from 1975	83/711	0.17	32	1.3 (1.1 to 1.7)	0.9 (0.7 to 1.2)	1.5 (1.1 to 1.9)	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.6)	0.7 (0.4 to 1.1)
Exposed from 1980	1/10	0.02	27	–	–	–	–	–	–
Exposed from 1990	0/5	0.04	20	–	–	–	–	–	–
Silica									
Men									
Unexposed workers	2956/32 361			1.0	1.0	1.0	1.0	1.0	1.0
Exposed from 1960	151/1018	0.10	35.0	1.6 (1.4 to 2.0)	1.4 (1.1 to 1.7)	1.9 (1.6 to 2.4)	1.6 (1.3 to 2.1)	1.2 (0.9 to 1.6)	1.0 (0.7 to 1.4)
Exposed from 1970	233/1487	0.08	26.0	1.7 (1.5 to 2.0)	1.4 (1.2 to 1.7)	1.9 (1.6 to 2.2)	1.5 (1.2 to 1.8)	1.5 (1.2 to 2.0)	1.3 (1.0 to 1.7)
Exposed from 1975	102/769	0.09	28.0	1.5 (1.2 to 1.8)	1.2 (0.9 to 1.5)	1.5 (1.2 to 2.0)	1.2 (0.9 to 1.6)	1.3 (0.9 to 1.9)	1.1 (0.8 to 1.6)
Exposed from 1980	85/729	0.07	26.0	1.3 (1.0 to 1.6)	1.1 (0.9 to 1.5)	1.2 (0.9 to 1.6)	1.1 (0.8 to 1.4)	1.4 (1.0 to 2.0)	1.3 (0.9 to 1.9)
Exposed from 1990	83/611	0.05	17.5	1.5 (1.2 to 1.8)	1.3 (1.0 to 1.7)	1.4 (1.0 to 1.8)	1.2 (0.9 to 1.6)	1.7 (1.1 to 2.4)	1.6 (1.1 to 2.4)
Women									
Unexposed workers	7558/77 370			1.0	1.0	1.0	1.0	1.0	1.0
Exposed from 1960	12/88	0.10	46.0	1.4 (0.8 to 2.6)	1.2 (0.7 to 2.3)	1.9 (1.0 to 3.5)	1.6 (0.8 to 3.1)	–	–
Exposed from 1970	9/72	0.18	35.0	1.3 (0.6 to 2.6)	1.1 (0.5 to 2.3)	1.4 (0.7 to 3.1)	1.1 (0.5 to 2.6)	–	–
Exposed from 1975	16/110	0.18	31.0	1.5 (0.9 to 2.5)	1.3 (0.7 to 2.2)	1.8 (1.0 to 3.2)	1.5 (0.8 to 2.7)	–	–
Exposed from 1980	16/152	0.05	27.0	1.1 (0.6 to 1.8)	0.9 (0.5 to 1.6)	1.2 (0.7 to 2.2)	1.0 (0.5 to 1.9)	–	–
Exposed from 1990	7/74	0.05	17.0	1.0 (0.4 to 2.1)	0.8 (0.4 to 1.8)	0.9 (0.4 to 2.3)	0.8 (0.3 to 2.0)	–	–

*Adjusted for county, age and index year.
†Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and silica were adjusted for each other.
RA, rheumatoid arthritis.

Table 4 OR of RA together with 95% CI for male workers classified as exposed to asbestos or silica exposure compared with workers classified as never exposed, by number of occupations* exposed (n=40 887)

	All RA cases					Seropositive RA		Seronegative RA	
	Cases/ controls	Median intensity for asbestos (fibre/cm^3) and silica (mg/m^3)	Median years since last occupation classified as exposed	Crude OR (95% CI) *	Adjusted OR (95% CI) †	Crude OR (95% CI) *	Adjusted OR (95% CI) †	Crude OR (95% CI) *	Adjusted OR (95% CI) †
Asbestos									
Unexposed workers	2151/24 033			1.0	1.0	1.0	1.0	1.0	1.0
One occupation	96/892	0.11	37	1.2 (1.0 to 1.5)	1.0 (0.8 to 1.3)	1.3 (1.0 to 1.7)	1.0 (0.8 to 1.4)	1.1 (0.8 to 1.6)	1.1 (0.7 to 1.5)
Two occupations	102/889	0.09	35	1.3 (1.1 to 1.6)	1.0 (0.8 to 1.3)	1.2 (1.0 to 1.6)	0.9 (0.6 to 1.2)	1.4 (1.0 to 2.0)	1.3 (0.9 to 1.9)
Three occupations	162/1142	0.09	34	1.6 (1.4 to 1.9)	1.3 (1.0 to 1.5)	1.8 (1.5 to 2.2)	1.3 (1.0 to 1.6)	1.3 (1.0 to .8)	1.2 (0.8 to 1.6)
Four occupations	169/1234	0.08	33	1.6 (1.3 to 1.9)	1.2 (1.0 to 1.5)	1.7 (1.4 to 2.1)	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.8)	1.1 (0.8 to 1.6)
Five occupations	74/467	0.09	33	1.8 (1.4 to 2.3)	1.4 (1.0 to 1.8)	1.8 (1.3 to 2.5)	1.4 (0.9 to 2.0)	1.8 (1.2 to 2.6)	1.5 (1.0 to 2.2)
Test for trend (p value)				<0.0001	0.0016	<0.0001	0.0075	0.0001	0.0596
Silica									
Unexposed workers	2956/32 361			1.0	1.0	1.0	1.0	1.0	1.0
One occupation	298/2355	0.10	31	1.4 (1.2 to 1.6)	1.2 (1.0 to 1.4)	1.5 (1.3 to 1.7)	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.5)	1.1 (0.9 to 1.4)
Two occupations	117/865	0.07	25	1.5 (1.2 to 1.8)	1.3 (1.1 to 1.6)	1.5 (1.2 to 1.9)	1.3 (1.0 to 1.7)	1.4 (1.0 to 2.0)	1.3 (0.9 to 1.9)
Three occupations	108/668	0.07	20	1.8 (1.5 to 2.2)	1.5 (1.2 to 1.9)	1.8 (1.4 to 2.3)	1.5 (1.1 to 2.0)	1.7 (1.2 to 2.4)	1.5 (1.1 to 2.2)
Four occupations	116/641	0.06	18	2.0 (1.6 to 2.4)	1.8 (1.4 to 2.3)	2.3 (1.8 to 2.9)	2.1 (1.5 to 2.8)	1.4 (1.0 to 2.1)	1.3 (0.9 to 1.9)
Five occupations	39/174	0.08	17	2.5 (1.7 to 3.5)	2.1 (1.4 to 3.1)	2.8 (1.8 to 4.2)	2.3 (1.4 to 3.8)	2.1 (1.2 to 3.7)	1.7 (0.9 to 3.1)
Test for trend (p value)				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0046

*Adjusted for county, age and index year.
†Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and silica were adjusted for each other.
‡One occupation corresponds to information on occupational title in one census. Censuses were carried out in 1960, 1970, 1975, 1980 and 1990.
RA, rheumatoid arthritis.

Table 5 OR of RA together with 95% CI among workers classified as exposed to different combinations of cigarette smoking and asbestos or silica compared with workers classified as never exposed (n=126 534).

	All RA cases					Seropositive RA	Seronegative RA
	Cases/controls	Median intensity for asbestos (fibre/cm^3) and silica (mg/m^3)	Median years since last occupation classified as exposed	Median pack-years	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*
Asbestos							
Men							
Never smoker/no asbestos exposure	671/9583				1.0	1.0	1.0
Never smoker/exposed to asbestos	124/1250	0.10	35	0	1.2 (0.7 to 2.2)	1.6 (0.8 to 3.2)	0.8 (0.3 to 2.1)
Smoker/no asbestos exposure	1480/14 450	0.00	–	16	2.2 (1.7 to 2.9)	3.3 (2.4 to 4.4)	1.0 (0.7 to 1.5)
Smoker/exposed to asbestos	479/3375	0.10	35	20	3.0 (2.0 to 4.4)	3.8 (2.4 to 6.1)	2.0 (1.1 to 3.5)
Women							
Never smoker/no asbestos exposure	2725/35 680				1.0	1.0	1.0
Never smoker/exposed to asbestos	5/32	0.02	33	0	4.4 (0.4 to 48.8)	–	–
Smoker/no asbestos exposure	4634/39 846	0.00	–	13	1.7 (1.5 to 1.9)	2.0 (1.7 to 2.3)	1.1 (0.9 to 1.3)
Smoker/exposed to asbestos	12/107	0.02	32	21	0.8 (0.2 to 3.2)	1.2 (0.3 to 4.7)	–
Men and women†							
Never smoker/no asbestos exposure	3396/45 263				1.0	1.0	1.0
Never smoker/exposed to asbestos	129/1281	0.10	35	0	1.1 (0.6 to 1.9)	1.2 (0.6 to 2.2)	0.9 (0.4 to 2.3)
Smoker/no asbestos exposure	6114/54 296	0.00	–	13	1.8 (1.6 to 2.0)	2.2 (1.9 to 2.4)	1.0 (0.9 to 1.3)
Smoker/exposed to asbestos	491/3482	0.10	35	20	2.4 (1.7 to 3.4)	2.6 (1.8 to 3.8)	2.0 (1.2 to 3.3)
Silica							
Men							
Never smoker/no silica exposure	870/12 245				1.0	1.0	1.0
Never smoker/exposed to silica	151/1399	0.07	21	0	1.1 (0.6 to 1.9)	1.3 (0.7 to 2.6)	0.7 (0.3 to 1.7)
Smoker/no silica exposure	2086/20 116	0.00	–	17	2.1 (1.7 to 2.6)	3.0 (2.3 to 4.0)	1.0 (0.7 to 1.4)
Smoker/exposed to silica	527/3304	0.08	26	20	2.9 (2.0 to 4.3)	4.1 (2.7 to 6.4)	1.4 (0.8 to 2.5)
Women							
Never smoker/no silica exposure	2769/36 286				1.0	1.0	1.0
Never smoker/exposed to silica	13/166	0.10	29	0	–	–	–
Smoker/no silica exposure	4789/41 084	0.00	–	13	1.7 (1.5 to 2.0)	2.0 (1.8 to 2.3)	1.1 (0.9 to 1.4)
Smoker/exposed to silica	51/366	0.10	29	19	2.2 (0.9 to 5.4)	2.7 (1.0 to 6.9)	1.3 (0.3 to 6.3)
Men and women†							

Continued

Table 5 Continued

	All RA cases					Seropositive RA	Seronegative RA
	Cases/controls	Median intensity for asbestos (fibre/cm^3) and silica (mg/m^3)	Median years since last occupation classified as exposed	Median pack-years	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*
Never smoker/no silica exposure	3640/48 532				1.0	1.0	1.0
Never smoker/exposed to silica	164/1565	0.07	25	0	0.8 (0.5 to 1.4)	0.9 (0.5 to 1.7)	0.7 (0.3 to 1.6)
Smoker/no silica exposure	6874/61 199	0.00	–	14	1.8 (1.6 to 2.0)	2.2 (1.9 to 2.5)	1.1 (0.9 to 1.3)
Smoker/exposed to silica	578/3670	0.08	26	20	2.5 (1.8 to 3.5)	3.1 (2.2 to 4.4)	1.4 (0.9 to 2.4)

*Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and silica were adjusted for each other.
†Additionally adjusted for sex.
RA, rheumatoid arthritis.

to silica had been smoking more compared with workers never exposed to silica.

DISCUSSION

In this study, we estimated the OR of developing RA associated with occupational exposure to asbestos and silica. Overall, we found that exposure to asbestos was associated with a risk increase in the order of 20% for both seropositive RA and seronegative RA and that the risk increase was particularly high among workers who were exposed to asbestos from 1970. Our study confirms earlier findings that silica is associated with an increased risk of RA. We extend that finding by demonstrating that, among men, this is seen in both major subsets of RA, and that the risk of seropositive RA increased with increasing exposure time.

Our study is the largest population-based study to explore the association between silicate minerals and RA with enough power to perform stratified analyses by sex. Another advantage is that we took potential confounding from the well-known risk factors alcohol and smoking into account. Since women to a lesser extent work in inorganic dust-related industries, less has been known about the risk of RA among women exposed to inorganic dusts. In our study less than 1% of women were considered exposed to asbestos or silica. Women overall had lower ORs than men, something that may be explained by the fact that women worked mainly in occupations where the intensity and duration of exposure to asbestos or silica were lower than those of men. The median intensity among workers in asbestos-exposed occupations was 0.02 fibre/cm^3 among women and 0.10 fibre/cm^3 among men. The Swedish threshold limit value for asbestos is 0.10 fibre/cm^3.[25 26] The JEM did not differentiate between male and female workers. It is therefore possible that the exposure level can differ by sex in certain occupations. Although the JEM is considered a valid instrument for assessing occupational exposures in large-scale studies, a disadvantage with this exposure measurement method is that it leads to non-differential misclassification of exposure, which, in turn, is likely to bias the strength of the studied associations towards the null value.

The knowledge about the relationship between asbestos and rheumatic diseases is scarce. Two observational studies on RA have been carried out in Sweden. The first one was a cohort study where the researchers found no increased risk among male workers.[4] The second study was a case-control study with 12 asbestos-exposed cases where an age-adjusted and smoking-adjusted OR of 2.5 (95% CI 1.0 to 6.8) was reported for incident RA.[5] In the present study we observed an increased risk of developing RA in the order of 20% among asbestos workers, both for seropositive and seronegative RA. The OR for RA was higher among asbestos-exposed workers before 1982 when asbestos was banned in Sweden. It may be that longer exposure duration and/or higher exposure intensity of asbestos is needed in order to trigger

development of RA. Since asbestos could have led to increased mortality from other diseases prior to enrolment into our study, our point estimates may be biased towards the null value.

The association between silica and RA has been shown in previous studies.[27–30] Earlier research has suggested that silica exposure is a risk factor mainly for seropositive RA,[10 28] but potentially also for seronegative RA.[27] In this larger study population we also observed a significantly increased risk for the smaller subset of seronegative RA, indicating that the mechanism responsible for disease development may be partly different from that of cigarette smoke, which is predominantly a risk factor for seropositive disease.[3 31] Our finding that the risk increases with duration of exposure among male workers has, to our knowledge, only been examined in one study previously.[27] The median intensity among workers exposed to silica was similar in men and women (0.08 mg/m^3 and 0.10 mg/m^3). The Swedish threshold limit value for silica is 0.10 mg/m^3.[25]

Concerning potential mechanisms, it is known that deposition of both asbestos and silica particles in the lungs may initiate an inflammatory response, including the release of proinflammatory cytokines and production of autoantibodies.[32] It is known that other inhaled agents, particularly cigarette smoke, triggers post-translational modifications of antigens by citrullination, and in prone individuals this can in turn result in immune reactions with antibody production against citrullinated peptides, which may then induce production of rheumatoid factor (anti-IgG), but these two types of antibodies are characteristic for seropositive RA.[1] Less is known about mechanisms that may be involved in the development of seronegative RA after harmful exposures to the lung, but the results indicate that inhalation of particles may also have a role there.[2]

According to the findings in the present study workers in occupations exposed to asbestos or silica are more likely to have been smokers, and also to have smoked more than workers not exposed to silicate minerals. Similarly, a Swedish cohort study of male construction workers showed that the proportion of smokers was higher among silica-exposed workers compared with workers not exposed to silica.[27] As was noted in our study, the relative risk of RA from exposure to silica was higher among smokers. We conclude that some workers in the construction industry exposed to the combination of silicate minerals and smoking have a particularly elevated risk of developing RA. This shows the need for preventive actions to be taken in such groups of workers.

In conclusion, our study shows that exposure to airborne agents such as asbestos and silica may contribute to the development of RA, in addition to previously described airborne exposures such as smoking. The fact that workers exposed to asbestos or silica often are also smokers demonstrates the need for preventive measures for RA, aimed at reducing occupational exposures for harmful airborne agents, as well as measures to reduce smoking in vulnerable groups of workers over the world.

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