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Occupational Exposure to Crystalline Silica and Risk of Systemic Lupus Erythematosus

A Population-Based, Case–Control Study in the Southeastern United States

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Objective. **Crystalline silica may act as an immune adjuvant to increase inflammation and antibody production, and findings of occupational cohort studies suggest that silica exposure may be a risk factor for systemic lupus erythematosus (SLE). We undertook this population-based study to examine the association between occupational silica exposure and SLE in the southeastern US.**

Methods. **SLE patients (n = 265; diagnosed between January 1, 1995 and July 31, 1999) were recruited from 4 university rheumatology practices and 30 community-based rheumatologists in 60 contiguous counties. Controls (n = 355), frequency-matched to patients by age, sex, and state of residence, were randomly selected from driver's license registries. The mean age of the patients at diagnosis was 39 years; 91% were women and 60% were African American. Detailed occupational and farming histories were collected by in-person interviews. Silica exposure was determined through blinded assessment of job histories by 3 industrial hygienists, and potential medium- or high-level exposures were confirmed through followup telephone interviews. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated by logistic regression.**

Results. **More patients (19%) than controls (8%) had a history of medium- or high-level silica exposure from farming or trades. We observed an association between silica and SLE (medium exposure OR 2.1 [95% CI 1.1–4.0], high exposure OR 4.6 [95% CI 1.4–15.4]) that was seen in separate analyses by sex, race, and at different levels of education.**

Conclusion. **These results suggest that crystalline silica exposure may promote the development of SLE in some individuals. Additional research is recommended in other populations, using study designs that minimize potential selection bias and maximize the quality of exposure assessment.**

Crystalline silica dust has been associated with systemic autoimmune diseases in humans, most notably with scleroderma, rheumatoid arthritis, and the small vessel vasculitides, and is one of the few environmental agents identified as a possible risk factor for systemic lupus erythematosus (SLE) (1–3). Commonly known as quartz, crystalline silica is an abundant mineral in rock, sand, and soil. The highest exposures to silica are known to occur in the dusty trades industries, such as mining, sandblasting, and quarrying, and in foundries and metal works, as well as in other jobs that use quartz-containing

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materials as a substrate or tool (4). Respirable silica exposure from farming may also exceed recommended and regulatory limits (5–7).

Much of the evidence relating silica exposure to SLE derives from case reports (8–10) and occupational cohort studies (1,2). Compared with estimated rates of SLE in the general population, higher rates of SLE have been described in two studies of silica-exposed workers: uranium miners (2) and workers in a scouring powder factory (1). Investigators in a population-based, registry-linkage study in Sweden also reported an increased risk of hospitalization with SLE in silicosis patients (relative risk 23.8, 95% confidence interval [95% CI] 10.3–47.0) (11).

Prolonged or acute exposure to very high levels of respirable silica dust (particles <5 μm) can cause pulmonary inflammation and fibrosis (silicosis) (12). Studies in humans and animals indicate that silica can act as an adjuvant to enhance the immune response nonspecifically (13–15), suggesting a potential mechanism by which silica could affect the development of autoimmune disease. Ingestion of silica activates macrophages, stimulating the secretion of proinflammatory cytokines (e.g., tumor necrosis factor and interleukin-1) (16). Silica exposure can also cause apoptosis (17,18), which may lead to the accumulation of intercellular debris that could drive an autoimmune response (19,20).

We describe herein a population-based, case–control study in the southeastern US that examined the role of occupational exposure to crystalline silica and SLE. Because career employment in the dusty trades industries is unusual among women, who constitute the majority of SLE patients, we were especially interested in the role of low-level exposures and short-term work experiences. Experience in agriculture is common in our study area; therefore, we also examined the relationship between SLE and silica exposure from farm work.

PATIENTS AND METHODS

Study participants. The Carolina Lupus Study is a population-based, case–control study in 60 contiguous counties of North Carolina and South Carolina. Patients were identified and referred through 30 community-based rheumatologists, 4 university rheumatology practices, public health clinics, and patient support groups. Patients were eligible for the study if they were diagnosed between January 1, 1995 and July 31, 1999, met the revised American College of Rheumatology criteria for SLE (21,22), were at least 18 years old, had lived in the study area for at least 6 months prior to diagnosis, and could speak and understand English.

Sex- and state-matched controls were identified through state driver's license records and were frequency-matched to patients in 5-year age groups. Eligibility criteria for controls were the same as those for patients, with the exception that controls had to have never been diagnosed as having lupus. Controls were randomly assigned a reference month and year to correspond to the frequency distribution of the diagnosis months and years of patients. Sample selection, recruitment, and enrollment procedures are described in greater detail elsewhere in this issue of *Arthritis & Rheumatism* (23). Study protocols were approved by the institutional review boards of the National Institute of Environmental Health Sciences and other participating institutions. The consent process did not reveal the study hypothesis pertaining to silica exposure.

The final sample consisted of 265 patients and 355 controls, with enrollment and participation of 93% of referred patients and 75% of screened and eligible controls. Among controls, contact and screening rates were considerably lower than participation rates. Of the 1,873 individuals who were selected from driver's license registries, 911 were ineligible due to invalid telephone numbers or addresses, leaving 962 potential controls eligible for screening. Of these, 163 (17%) refused screening, 195 (20%) were ineligible (deceased or did not meet eligibility criteria), 129 (13%) were deferred based on the study protocol, and 120 (12%) refused to participate.

Data collection. Data were collected during a structured 60-minute, in-person interview. For patients, clinical features observed and results of laboratory tests performed within 6 months of diagnosis were collected through standardized chart reviews (24). Serum samples were also obtained from 92% of patients for measuring autoantibodies by standard methods. A detailed lifetime work history was taken of all jobs held for at least 12 months, including farm work. Seasonal work was included if the cumulative duration of work at the job was at least 12 months. Verbatim responses were recorded for job title, industry, and main tasks, and information on the year started and ended, hours per week, months per year, and the use of personal protective equipment, such as dust masks or respirators, was collected for each job. Additional questions were asked about work in several specific occupations or industries likely to have high-level silica exposure, including jobs of <12 months' duration. The questions asked concerned sandblasting or abrasive grinding of rock or stone, stone or brick masonry, mining, and the manufacture of pottery, ceramics, glass, or abrasive cleansers. We also asked about grinding of glass or other materials and about silica-containing materials (i.e., clay, enamel, tile, abrasive cleansers) used at least once per week at any job.

We collected information about experience of any duration on a farm during the following age ranges: 10–15 years, 16–19 years, 20–39 years, and $\geq$40 years. The farming history included farm location (state and county), major crops grown, and the number of days per week and hours per day worked during harvest time and during other times. Questions were also asked about pesticide mixing and application.

Exposure assessment. *Trades*. Silica exposure from the dusty trades and other nonfarming jobs (subsequently referred to as "trades") was estimated by expert assessment with blinding as to case–control status and demographic characteristics. Complete data from the lifetime job histories were reviewed by one of the authors (CGP) and compared with published lists of industries, jobs, tasks, and materials known

for silica exposure (4,25–27). Ninety-five percent of the study participants had held one or more jobs lasting at least 12 months. A total of 2,196 jobs were reported (mean per participant 3.7), and 198 of these jobs (9%) were selected for evaluation by industrial hygienists based on their potential for silica exposure. Three industrial hygienists (LAN-F, WTS, JMD) independently estimated silica exposure based on a blinded review of the verbatim lifetime job history data and considering corroborating evidence from job- and material-specific questions. Positive responses to the specific job/task list, including work of <12 months' duration, were reviewed by an industrial hygienist (LAN-F).

Industrial hygienists assigned each job a level of average exposure intensity (high, moderate, low, or no) for usual tasks, which took into consideration the likely concentration and frequency of exposure during the average work week. Estimates of high and moderate intensity were based on personal exposure limits for crystalline silica in the workplace, published by the National Institute of Occupational Safety and Health (NIOSH) and by the Occupational Safety and Health Administration (28,29). Low exposure intensity was defined as exposure below the limit recommended by NIOSH. Jobs with silica exposure at or below levels experienced by the general population were considered to provide no additional exposure. The industrial hygienists also assigned each intensity rating a certainty score (high, moderate, or low) based on the information provided, the type of work, and the industrial hygienists' personal knowledge of the exposures in each job.

Farm work. To assess potential silica exposure from farming, experts in agromedicine and industrial hygiene developed a dust-exposure matrix specific to farming practices in the study area based on information provided by state agriculture extension agents. Dust exposure from farming was estimated as low or moderate for most tasks, with the highest exposures expected from harvesting peanuts and mechanized planting of tobacco or sweet potato seedlings. Soil type is another determinant of silica exposure from farm work: in North Carolina, sandy and sandy-loam soils have higher proportions of respirable quartz than do clay soils (30). Thus, using soil systems maps (31), farm location was used to infer soil type and relative differences in percent respirable silica in soil dust.

Followup interviews. We conducted highly structured telephone interviews to collect further information on jobs initially rated by the expert panel as high or moderate in exposure intensity, including specific jobs lasting <12 months. Individualized questionnaires were designed to confirm previously reported data and to examine specific tasks related to silica exposure and the frequency and duration of such tasks, the work environment, dust control measures, and the use of dust masks or respirators. We also conducted followup interviews to confirm farm history data and to collect additional information on experience with specific dusty tasks. Participants were eligible for the followup interviews if they reported working on a farm for at least 12 months, and if they reported working a minimum of 20 hours per week during harvest time and either tractor use or mechanized planting or working with peanuts or sweet potatoes as a main task on the job history, or peanuts or sweet potatoes as a major crop.

Based on these eligibility criteria, 180 subjects (96 patients and 84 controls) were identified as candidates for followup interviews, and 149 subjects (83%) were interviewed. Six patients were unable to participate due to death or illness, 4 controls declined to participate, and 12 patients and 9 controls were otherwise lost to followup.

Exposure indices. The final exposure assignments for silica exposure from trades were derived by consensus of two of the authors (LAN-F, CGP) using all available data from the original and followup interviews to confirm or adjust intensity and certainty estimates. Based on previous population-based studies of occupational exposures using a combination of intensity and certainty ratings (32), participants were divided into 4 exposure groups: high, medium, low, and no. High exposure was defined as a rating of "high intensity and high or moderate certainty" or "moderate intensity and high certainty," including exposure in sandblasting, mining, stone or brick masonry, pottery or ceramics manufacture, or in other jobs. Medium exposure was defined as a rating of "high intensity and low certainty," "moderate intensity and low or moderate certainty," or "low intensity and high certainty," including exposure in grinding glass, plastic, or other materials, or in either spraying or sanding enamel. Low exposure was defined as a rating of "low intensity and moderate or low certainty," including exposure from the daily use of abrasive cleansers in janitorial occupations (e.g., hotels) as well as exposure to minimally processed cotton dust in textile work. Exposure group assignment was based on the highest level–exposure job for each individual. The high–average exposure group for trades contained <1% of patients and controls and was thus combined with the medium-exposure group in some analyses.

To estimate silica exposure from farming, we considered data on dusty tasks, farm location, and soil systems maps. Analyses presented here limit the consideration of location and tasks to participants who worked in farming for a total of at least 12 months and 40 hours per week. The high-exposure group included those who reported work on a farm in the sandy-soil zone and frequent dusty tasks (harvesting peanuts or mechanical transplanting in excess of the median hours per week for controls). The medium-exposure group included those who reported infrequent dusty tasks and work on a farm in the sandy-soil zone, or those who reported frequent dusty tasks and work on a farm not located in the sandy-soil zone. The low-exposure group included those who reported infrequent dusty tasks and work only in other soil types, or none of the dusty tasks mentioned above.

A joint index for silica exposure from farming and trades was also developed, assuming rough equivalence between the low-, medium-, and high-exposure groups for trades and farming. The very low–exposure group included only farming between 20 hours and 40 hours per week, or farming of <12 months' cumulative duration. The high- and medium-exposure groups for trades and farming were combined for analyses of effect modification, duration, and timing.

Statistical analysis. Potential confounders are factors that are independently associated with both the exposure and the disease, which can bias the estimated exposure effect if not accounted for during analyses. Demographic factors that might be related to occupational silica exposure in this study include race, education, age, and sex. Frequency-matching, as performed in this study for age and sex, can increase the efficiency of a study when there is an imbalance in the frequency of a potential confounder between case and control populations (e.g., 90% of SLE patients are women, almost twice the

Table 1. Demographic characteristics of patients and controls in the Carolina Lupus Study*

	Patients (n = 265)	Controls (n = 355)
Sex		
Female	240 (91)	321 (90)
Male	25 (9)	34 (10)
Race		
African American	160 (60)	99 (28)
White	89 (34)	230 (65)
Other†	16 (6)	26 (7)
Education		
Less than high school	59 (22)	32 (9)
Completed high school	66 (25)	77 (22)
Some college	80 (30)	130 (37)
Completed college	60 (23)	116 (33)
Age in years‡		
15–24	43 (16)	44 (12)
25–34	86 (33)	103 (29)
35–44	49 (19)	76 (21)
45–54	46 (17)	72 (20)
55–64	24 (9)	35 (10)
65–81	17 (6)	25 (7)
State		
North Carolina	205 (77)	252 (71)
South Carolina	60 (23)	103 (29)

* Values are the number (%).
† Includes American Indians, Asians, and Hispanics.
‡ At diagnosis for patients or assigned reference age for controls.

percentage of women in the general population). However, matching is not necessary to achieve an unbiased estimate if there is sufficient representation of the factor in cases and controls (33). Race is an example of such a factor in this study. The effect of the confounder can be accounted for by including the variable in logistic regression models or by examining the results stratified by different levels of the confounding variable.

Silica exposure was evaluated separately for trades and farm work and then in combined analyses. All odds ratios (ORs) and 95% CIs presented here were estimated by unconditional logistic regression, adjusting for the frequency-matching variables (age, sex, and state), race (white and nonwhite), and education (less than high school, high school graduate, some college or technical school, college graduate). Exposure effects were estimated as categorical variables representing each exposure group. Statistical tests for trend involved the creation of single ordinal variables with even spacing representing the different exposure groups (e.g., 0 = no, 1 = low, 2 = medium, 3 = high).

Stratified analyses were conducted by sex, race (African American or white), education at 2 levels (≤12 years or >12 years), and smoking (ever or never smoked regularly [at least 1 cigarette per day for 3 months]). We evaluated the interaction of silica exposure and smoking on a multiplicative scale, comparing likelihood ratio models and the chi-square statistic, and by estimated joint effects models. We also examined possible confounding by pesticide exposure (ever applied or mixed pesticides, and frequency). Pesticide mixing was evaluated in models for men only, since there were only 3 women with a history of pesticide mixing.

To evaluate latency and time of effect, we examined moderate- or high-level silica exposure across 4 categories of time (0–4 years, 5–19 years, 20–39 years, and ≥40 years) prior to the date of diagnosis in patients and the reference date in controls. Depending on the duration of exposure, a participant could be classified as having been exposed in any or all categories. Analyses were also conducted for cumulative duration of medium or high silica exposure (<12 months, 12–59 months, 60–119 months, and ≥120 months).

The relation between silica exposure and specific clinical features or autoantibodies among patients was evaluated using unconditional logistic regression, as described above. Models were also adjusted for referral from university versus community clinics to account for possible differences in patient characteristics or physician practices (e.g., frequency of ordering tests).

RESULTS

The demographic characteristics of Carolina Lupus Study participants are shown in Table 1. Ninety-one percent of patients were women, 60% were African American, 34% were white, and 6% were from other ethnic groups (Hispanics, Asians, and American Indians). The racial distribution of controls (28% African American, 65% white, and 7% "other") reflected that of the general population in the study area. The mean age at diagnosis was 39 years (range 15–81 years), and the age distribution was similar in patients and controls. More patients than controls (22% versus 9%; $P < 0.0001$) had less than a high school education, which was accounted for in multivariate analyses as described.

Based on the expert assessment of respirable

Table 2. Prevalence of occupational silica exposure from work in the dusty trades or other nonfarming jobs, in SLE patients and controls*

Exposure rating	Patients (n = 265)	Controls (n = 355)	OR (95% CI)†
Any experience‡			
None	217 (82)	322 (91)	Referent
Low	24 (9)	20 (6)	1.6 (0.8–3.3)
Medium or high	24 (9)	13 (4)	3.1 (1.4–7.0)§
≥1 year experience			
None	228 (86)	325 (92)	Referent
Low	22 (8)	18 (5)	1.5 (0.7–3.1)
Medium or high	15 (6)	12 (3)	1.9 (0.8–4.7)

* Values are the number (%). SLE = systemic lupus erythematosus; OR = odds ratio; 95% CI = 95% confidence interval. Participants exposed at >1 job are grouped based on their highest job rating. Fewer than 1% of patients and controls (n = 5) were rated high for any exposure.
† Calculated by unconditional logistic regression modeling and adjusted for age, sex, race, education, state, and farm work.
‡ Includes any work experience of <1 year in specific silica-related jobs or industries.
§ $P = 0.003$ by trend test for 3-level variable.

Table 3. Experience in farm work among patients and controls, stratified by frequency, duration, soil type, and dusty tasks*

Exposure group	Patients (n = 265)	Controls (n = 355)	OR (95% CI)†
Never lived or worked on a farm	146 (55)	215 (61)	Referent
Ever lived or worked on a farm	119 (45)	140 (39)	1.0 (0.7–1.4)
Worked <40 hours/week‡	49 (18)	85 (24)	0.7 (0.5–1.1)
Worked ≥40 hours/week			
<12 months	22 (8)	22 (6)	1.0 (0.5–2.0)
≥12 months	48 (18)	33 (9)	1.7 (1.0–3.0)
Worked ≥40 hours/week for ≥12 months			
Soil type zone§			
Clay, mixed	22 (8)	18 (5)	1.5 (0.7–3.0)
Sandy	26 (10)	15 (4)	2.2 (1.2–4.7)
Dusty task group¶			
Low, moderate	32 (12)	26 (7)	1.5 (0.8–2.8)
High	16 (6)	7 (2)	3.0 (1.1–8.2)#

* Values are the number (%). See Table 2 for definitions.
† Calculated by unconditional logistic regression modeling and adjusted for age, sex, state, race, and education.
‡ Never worked at least 40 hours per week during months worked on a farm.
§ Based on farm location. The clay and mixed zone includes farm work limited to the Piedmont, Coastal Plain, and areas outside of North Carolina and South Carolina. The sandy zone includes any farm work in the Sandhills region of North Carolina.
¶ Task groups were assigned based on followup interviews. The high task group includes peanut harvesting and mechanical transplanting of tobacco or sweet potatoes exceeding the median hours per year in controls. The low and moderate group includes all other low-frequency peanut harvesting and mechanical transplanting, all tractor driving, and other unspecified farm tasks.
# $P = 0.05$ by trend test for 3-level variable.

silica dust exposure, 37 participants (6%) reported a history of medium- or high-level exposure from trades. Exposure was more common in men (29%) than in women (4%), especially in jobs related to the construction industry, but women were represented in all exposure groups listed, including mining, sandblasting, and stone masonry. Patients were more likely than controls to report a history of silica exposure: medium- or high-level exposure of any duration was associated with a 3-fold increased risk of SLE (Table 2). A weaker association (OR 1.9) that was not statistically significant was seen in analyses limited to jobs of at least 12 months' duration.

Farm work was a common experience in our study population (Table 3). Although there was no increased risk for having lived or worked on a farm, we observed a positive association (OR 1.7) for having worked at least 40 hours per week for at least 12 months. This association was slightly stronger for work on farms in sandy soils (OR 2.2) and for performing very dusty tasks, such as peanut harvesting and mechanical transplanting (OR 3.0). More patients (4%) than controls (1%) reported both dusty tasks and work in the Sandhills region, but due to the low numbers in these groups, the estimated effect was highly imprecise (OR 6.7, 95% CI 1.3–36.1). Pesticide use did not appear to confound the associations observed for farm work. We observed an elevated and highly imprecise association for pesticide mixing (OR 8.6, 95% CI 1.7–43.6), but not for applying pesticides (OR 1.2, 95% CI 0.6–2.3). The prevalence of mixing pesticides was extremely low among women (<1%), and among men the independent effect of farming was only slightly attenuated (15%) after adjustment for pesticide mixing.

Table 4 presents the frequency of silica exposure from farming and trades combined compared with no silica exposure from either source, both for all participants and stratified by sex, education, and race. We observed the strongest association for the high-exposure group (OR 4.6) compared with the medium- and low-exposure groups (ORs of 2.1 and 1.6, respectively). The very low–exposure group showed a slight inverse association (OR 0.7). Across these 4 exposure groups, we observed a monotonic increase in effect ($P = 0.002$). Estimated associations were similar in subgroup analyses, but were less precise due to smaller sample sizes. Although exposure frequencies varied by sex, the associations between SLE and silica exposure were seen in

Table 4. Association between SLE and silica exposure from farming and trades combined*

Exposure group†	Patients (n = 265)	Controls (n = 355)	OR (95% CI)‡
All participants			
None	126 (48)	199 (56)	Referent
Very low	54 (20)	96 (27)	0.7 (0.5–1.0)
Low	34 (13)	30 (8)	1.6 (0.9–3.0)
Medium	38 (14)	25 (7)	2.1 (1.1–4.0)
High	13 (5)	5 (1)	4.6 (1.4–15.4)
Women			
None	121 (50)	187 (58)	Referent
Very low	54 (23)	92 (29)	0.7 (0.5–1.1)
Low	29 (12)	22 (7)	1.5 (0.8–2.9)
Medium	29 (12)	18 (6)	2.0 (1.0–4.0)
High	7 (3)	2 (1)	3.3 (0.6–17.8)
Men			
None	5 (20)	12 (35)	Referent
Very low	0 (0)	4 (12)	NC
Low	5 (20)	8 (24)	1.9 (0.4–9.7)
Medium	9 (36)	7 (21)	3.0 (0.6–16.7)
High	6 (24)	3 (9)	6.0 (0.7–48.0)
≤12 years' education			
None	45 (36)	43 (39)	Referent
Very low	29 (23)	39 (36)	0.5 (0.2–1.0)
Low	18 (14)	12 (11)	0.9 (0.3–2.7)
Medium	25 (20)	12 (11)	2.1 (0.8–5.4)
High	8 (6)	3 (3)	2.5 (0.5–13.1)
>12 years' education			
None	81 (58)	156 (63)	Referent
Very low	25 (18)	57 (23)	0.9 (0.5–1.5)
Low	16 (11)	18 (7)	2.1 (1.0–4.6)
Medium	13 (9)	13 (5)	1.9 (0.8–4.5)
High	5 (4)	2 (1)	6.6 (1.0–42.6)
African American			
None	69 (43)	46 (46)	Referent
Very low	37 (23)	36 (36)	0.6 (0.3–1.3)
Low	23 (14)	11 (11)	1.3 (0.5–3.1)
Medium	25 (16)	5 (5)	3.8 (1.2–11.9)
High	6 (4)	1 (1)	5.8 (0.6–59.3)
White			
None	46 (52)	137 (60)	Referent
Very low	16 (18)	53 (23)	0.8 (0.4–1.6)
Low	10 (11)	19 (8)	1.6 (0.7–4.0)
Medium	11 (12)	18 (8)	1.7 (0.7–4.1)
High	6 (7)	3 (1)	5.3 (1.1–26.5)

* Values are the number (%). Included are 240 female patients, 321 female controls, 25 male patients, 34 male controls, 125 patients and 109 controls with ≤12 years' education, 140 patients and 246 controls with >12 years' education, 160 African American patients, 99 African American controls, 89 white patients, and 230 white controls. See Table 2 for other definitions.

† Subjects are grouped by highest exposure. The high group includes high exposures from both farming and trades. The moderate group includes moderate exposures from both farming and trades. The low group includes low exposures from both farming and trades. The very low group includes those who farmed at least 20 hours per week, but who are not included in any higher exposure group.

‡ Estimated by logistic regression adjusted for age, sex, state, race, and education. Since there were no male patients in the very low–exposure group, an adjusted OR could not be calculated (NC). The crude OR and 95% CI were estimated by adding 1 count per cell (OR 0.15, 95% CI 0.01–1.5).

women and men. Silica exposure was less common among participants with more than a high school education, but associations between silica and SLE were observed at both higher and lower education levels. The associations of silica and SLE were also seen in both whites and African Americans.

Although smoking was not associated with SLE overall, the association between silica and SLE was greatest among those who had ever smoked regularly (OR 6.7) (Table 5). The joint effect of smoking and medium or high silica exposure (OR 2.7) was stronger than expected, based either on the independent effect of smoking in those with very low exposure (OR 0.6) or on the independent effect of medium or high silica exposure without smoking (OR 1.4). This represents a statistically significant interaction ($\chi^2 = 4.27$, $P = 0.039$).

There were no clear patterns of exposure timing or duration related to risk of SLE (data not shown). We saw no differences in the effects of medium- or high-level exposure across 4 periods of time (0–4 years, 5–19 years, 20–39 years, and ≥40 years) prior to diagnosis, controlling for work in other time periods. The majority of patients reported diagnosis within 5 years of the onset of symptoms, and the associations between silica and SLE persisted when exposures during this time frame were excluded.

The frequency of most clinical signs and symptoms was the same in silica-exposed patients (medium- or high-exposure groups) as in those with no silica exposure (Table 6). However, hemolytic anemia and leukopenia were less common in silica-exposed patients (ORs of 0.1 and 0.3, respectively). There were no statistically significant differences in the prevalence of autoantibodies in the silica-exposed patients compared with the unexposed patients (Table 6), but adjusted analyses suggested positive associations of silica with anti-DNA antibodies and anti-Sm, and inverse associations with anti-La and anticardiolipin antibodies.

DISCUSSION

In this population-based, case–control study, we found that occupational exposure to crystalline silica dust was associated with the development of SLE. This association appeared strongest for those in the high- or medium-exposure groups, and we saw little evidence suggesting differences in effect by sex, race, or education level.

Silica has been linked to several systemic auto-

Table 5. Association of SLE with silica exposure from farming and trades in those who ever or never smoked at least 1 cigarette per day for 3 months: stratified and joint effects*

Silica exposure	Never smoked			Ever smoked		
	Patients (n = 162)	Controls (n = 179)	OR (95% CI)†	Patients (n = 103)	Controls (n = 176)	OR (95% CI)†
None	87 (54)	100 (56)	Referent	39 (38)	99 (56)	Referent
Very low	35 (22)	50 (28)	0.8 (0.5–1.5)	19 (18)	46 (26)	0.6 (0.3–1.3)
Low	21 (13)	14 (8)	1.6 (0.7–3.7)	13 (13)	16 (9)	1.8 (0.7–4.4)
Medium	15 (9)	13 (7)	1.5 (0.6–3.7)	23 (22)	12 (7)	3.6 (1.5–8.9)
High	4 (2)	2 (1)	2.7 (0.4–19.5)	9 (9)	3 (2)	6.7 (1.4–32.3)
Joint effects models						
None, very low, and low	143 (88)	164 (92)	Referent	71 (69)	161 (91)	0.6 (0.4–1.0)
Medium or high	19 (12)	15 (8)	1.4 (0.7–3.1)	32 (31)	15 (9)	2.7 (1.3–5.7)

* Values are the number (%). See Table 2 for definitions.
† Estimated by logistic regression adjusted for age, sex, state, race, and education.

immune diseases, including scleroderma, rheumatoid arthritis, and the small vessel vasculitides (e.g., Wegener's granulomatosus) (3). Most evidence for this relationship has come from studies of occupational cohorts (mostly men) with very high-level and long-term exposure to silica, and from population-based studies that used silicosis as a surrogate for high-level exposure (also mostly men, due to their preponderance in the dusty trades). Few studies have included women, and most do not provide evidence of an association in women (34–37). Although career employment in the dusty trade industries is uncommon in women, we hypothesized that women might have alternative sources of silica exposure or be more likely to hold short-term or part-time jobs. Women might also work at jobs with short high-level silica exposure but low average exposures.

Table 6. Prevalence of autoantibodies and clinical features in SLE patients with and those without silica exposure*

	Silica exposure		OR (95% CI)†
	High/medium	None	
Autoantibodies‡			
ANAs§	45 (94)	120 (98)	0.8 (0.1–5.2)
Anti-DNA	13 (27)	33 (27)	2.2 (0.8–5.9)
aCL	3 (6)	17 (14)	0.4 (0.1–1.7)
Anti-Sm	8 (17)	13 (11)	2.3 (0.7–8.0)
Anti-Ro	15 (31)	46 (37)	0.8 (0.3–1.8)
Anti-La	5 (10)	10 (8)	0.3 (0.1–1.5)
Anti-RNP	14 (29)	36 (29)	1.3 (0.5–3.5)
Clinical features¶			
Malar rash	23 (46)	53 (40)	1.2 (0.6–2.6)
Discoid rash	9 (18)	18 (14)	1.1 (0.4–3.3)
Photosensitivity	22 (44)	51 (38)	0.9 (0.4–2.0)
Oral ulcers	10 (20)	23 (17)	1.6 (0.6–4.3)
Arthritis	39 (78)	100 (75)	0.9 (0.4–2.3)
Serositis	21 (42)	53 (40)	1.3 (0.6–2.7)
Pleuritis	18 (36)	47 (35)	1.3 (0.6–2.8)
Pericarditis	6 (12)	19 (14)	1.0 (0.3–3.1)
Renal	13 (26)	31 (23)	1.7 (0.7–4.0)
Neurologic	1 (2)	11 (8)	0.3 (0.0–2.9)
Anemia	1 (2)	18 (14)	0.1 (0.0–0.5)
Leukopenia	5 (10)	25 (19)	0.3 (0.1–1.0)
Lymphopenia	12 (24)	28 (21)	0.9 (0.3–2.7)
Thrombocytopenia	6 (12)	15 (11)	0.6 (0.2–2.8)

* Values are the number (%). ANAs = antinuclear antibodies; aCL = anticardiolipin antibodies (see Table 2 for other definitions).
† Estimated by logistic regression adjusted for age at diagnosis (<30 years, 30–49 years, ≥50 years), sex, race (white and nonwhite), education, and referral from university clinic.
‡ From 48 patients with and 123 patients without silica exposure.
§ Adjusted for age, race, and referral from university clinic due to small number of ANA-negative patients.
¶ From 50 patients with and 123 patients without silica exposure.

The association between silica and SLE was stronger when short-term exposures (<12 months) were included. Recall bias does not appear to explain this observation. Patients were unlikely to have known about the study hypothesis. Patients and controls reported the same number of jobs (average of 3.6 and 3.8 jobs, respectively) in the job history, and patients did not report more short-term work experience compared with controls for solvent-related jobs. Few studies have specifically evaluated recall bias and occupational histories. A recent study of occupational exposures and cancer indicated that, while patients were more likely to volunteer information, there was little evidence of differential recall for prompted questions (38). Initial and followup interviews in the Carolina Lupus Study were highly structured and involved specific prompting of job histories and silica-related jobs or tasks. Volunteered information (i.e., information that was not elicited in response to a specific question) was not used to assess potential for silica exposure. Two recent studies suggest that reporting of farm work is fairly reliable (39,40), but

some subgroups may have more difficulty in accurately recalling their experiences (e.g., older or less-educated patients) (40).

Selection bias might also explain the excess of short-term, silica-related jobs reported by patients compared with controls. To account for our results, the probability of being a control would have to be strongly and inversely associated with the probability of being exposed to silica. Because high-level exposure is relatively uncommon in the general population and in women especially, our results may be sensitive to a lack of participation of, or contact with, silica-exposed individuals. Controls most likely to work in silica-related jobs might have been overlooked by selection procedures using driver's license registries, perhaps being less likely to drive or register for identification cards, or perhaps being more transient. However, investigators in a recent study of African Americans living in several rural counties in eastern North Carolina reported that driver's license registries had relatively complete coverage (at least 90%) compared with census estimates (41).

We saw no difference in effect when analyses were stratified using education as a proxy for economic status and social behavior, factors that might predict selection into the study sample. This decreases the likelihood that selection bias could account for the observed results. Results were also similar when patients without driver's licenses were excluded (data not shown). In a study of breast cancer in a similar population in North Carolina that used a similar control recruitment method, contact rates were lowest and refusal rates were highest among younger African American controls (42). However, in our study, silica-exposed participants were more likely to be older (median age 55 years), and there was no difference by case–control status.

In order for a variable to confound the observed association between silica and SLE, the association between the exposure and SLE must be at least as strong as the silica–SLE association. We are unaware of any exposures in the present study or in other studies that are independently and strongly associated with both silica exposure and SLE that could account for the association we observed. Pesticide mixing was associated with SLE, but did not appear to confound the relationship between indices of silica exposure and SLE. However, these analyses were based on very small numbers. Subsequent analyses on the frequency of pesticide application, a more common experience, failed to show an association independent of the silica dust exposure indices (data not shown).

Occupational studies of silica exposure and scleroderma support the idea that exposure intensity (e.g., concentration and frequency) is more important than cumulative exposure or duration (43,44). Short-term, high-level exposures may overwhelm lung clearance mechanisms, increasing the amount of silica internalized and relocated to organs such as lymph nodes or kidney. In a recent study of experimental silicosis, lung-associated lymph nodes were the primary source of increased systemic levels of IgG and IgM (45).

We observed little difference in the association between silica and SLE in women compared with men, within the limits of sample size. Women were less likely than men to be classified in the medium- or high-exposure groups: 15% of female patients reported any work experience in trades or farming in the medium– or high–silica exposure groups compared with 60% of male patients. Women were more likely than men, however, to report silica-related jobs held for <12 months. The prevalence of female controls with long-term (≥ 12 months), high-level silica exposure from trades (3%) was similar to the prevalence of silica exposure reported by investigators in two recent population-based studies of scleroderma in women in the US (35,36).

To the best of our knowledge, this is the first epidemiologic study to specifically examine farm work as a source of silica exposure. We used information on dusty tasks and farm location as well as soil systems maps to estimate differences in potential silica exposure. We observed no marked difference in the prevalence of different crops by soil type, but participants who farmed in the Sandhills region were more likely to report a history of the dustiest tasks (e.g., harvesting peanuts, mechanical transplanting).

The association we observed for the high- or medium-exposure groups was stronger among those who had ever smoked regularly. Of those who smoked, 69% of patients and 60% of controls smoked concurrently with silica exposure. These findings should be interpreted cautiously, considering the imprecision of the effect estimates. However, this hypothesis is consistent with several plausible mechanisms. Pulmonary immune processes are complex (46), and the effects of smoking on the immune response are likewise multifaceted. Smoking may affect the clearance of silica as well as the response to silica that remains in the lung (47,48). Smoking can increase leukocyte and monocyte populations and the concentration of soluble intercellular adhesion molecule 1 (49), a glycoprotein involved in the recruitment of cells into tissues undergoing inflammatory responses. Finally, the polyphenol-rich tobacco

glycoprotein, isolated from cured tobacco leaves, is a B cell mitogen in mice, can stimulate T cell proliferation and B cell differentiation in humans (50), and can also activate the classical complement pathway (51).

Our analyses revealed no predominant time window of exposure that accounted for the association we observed between silica and SLE. The theory that silica acts as an adjuvant provides little indication of whether silica exposure would require a long latency or, conversely, whether the relevant exposures would be limited to the recent years before disease onset. Internalized silica has been shown to persist in humans with high-level exposures (52). Thus, there may be a broad window of exposure, unrelated to the time during which silica acts as an adjuvant, to amplify autoimmune disease processes triggered by other events or agents.

It is difficult to draw conclusions about disease phenotype among exposed versus unexposed cases, given the small numbers that are present after stratification by exposure. Previous reports describe inconsistent findings regarding the clinical features of silica-exposed lupus patients (1,2,9). Silica exposure has been associated with various forms of renal disease (53–56), but we did not observe an increase in the frequency of renal disease among silica-exposed patients in this study. Hogan et al recently reported no association between silica and lupus nephritis (57). However, the mechanisms involved in lupus nephritis, which typically involve complement deposition, may differ from those in other silica-mediated renal pathology. In our analyses, we found that lower risk of leukopenia was independently associated with silica exposure. An explanation for this observation could be that silica stimulates the production of some subsets of white blood cells, resulting in a lower prevalence of leukopenia (the decrease in white blood cells overall) but not lymphopenia (the decrease of lymphocytes, e.g., T cells and B cells). Mechanisms that could explain the inverse association with hemolytic anemia are less clear.

As in any study that relies on voluntary participation, we cannot rule out the possibility that selection bias could have affected the association we observed. Recall bias is also a consideration, although we saw no indication of differential recall of occupational histories between patients and controls. We cannot estimate the effect on our results of uncontrolled confounding by selection or recall bias. Investigators in two other studies in highly exposed groups reported strong associations between silica exposure and the risk of developing SLE (1,2) or the risk of SLE-related hospitalization (11). A prospective cohort study design would be ideal for reducing potential bias due to control selection and participation, but would be difficult to conduct in a general population setting for both a relatively rare exposure and a rare disease.

Attention in future studies should also be given to conducting a rigorous and unbiased exposure assessment, thus reducing the impact of exposure misclassification. Our experience suggests that questions should cover a broad range of exposure sources, including short-term employment and work outside the traditional dusty trades. Because this is the first population-based study to examine crystalline silica exposure and SLE, the consistent associations we observed are informative. Results were based on a blinded expert assessment of extensive work history data, including followup interviews to refute or confirm potential exposures and reduce the likelihood of false-positive exposure misclassification. Farm work was included as a source of silica exposure, thus improving exposure classification for a population in which farm experience is common.

The population-attributable risk represents the proportion of cases that might be prevented if the exposure was eliminated. This measure is influenced by the strength of the exposure–disease association and by the prevalence of the exposure in the population (see formula 2.15 in ref. 58). Assuming that high or medium silica exposure confers a 2.8-fold increased risk for both women and men, and based on an exposure prevalence in controls of 7% for women and 41% for men, the population-attributable risk in our study population can be estimated to be 0.11 for women and 0.42 for men.

Similar to the complex genetic risk factors for SLE, there are likely to be a variety of environmental exposures that may initiate or promote the development of SLE. The results of this study support the investigation of other potential immune adjuvants or factors that might affect apoptosis in SLE and other autoimmune diseases. In conjunction with experimental and clinical studies, epidemiologic research may be used to advance models of autoimmune disease etiology and to identify factors involved in the initiation and progression of disease.

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