Long-term Exposure to Crystalline Silica and Risk of Heart Disease Mortality

Yuewei Liu,[a,b] *Yi Rong,*[a] *Kyle Steenland,*[c] *David C. Christiani,*[d] *Xiji Huang,*[a] *Tangchun Wu,*[a] *and Weihong Chen*[a]

Background: The association between crystalline silica exposure and risk of heart disease mortality remains less clear.

Methods: We investigated a cohort of 42,572 Chinese workers who were potentially exposed to crystalline silica and followed from 1960 to 2003. Cumulative silica exposure was estimated by linking a job-exposure matrix to each person's work history. Low-level silica exposure was defined as never having held a job with an exposure higher than 0.1 mg/m^3. We estimated hazard ratios (HRs) in exposure–response analyses using Cox proportional hazards model.

Results: We identified 2846 deaths from heart disease during an average of 35 years follow-up. Positive exposure–response trends were observed for cumulative silica exposure associated with mortality from total heart disease (HRs for increasing quartiles of cumulative silica exposure compared with the unexposed group = 0.89, 1.09, 1.32, 2.10; *P* for linear trend < 0.001) and pulmonary heart disease (0.92, 1.39, 2.47, 5.46; *P* for linear trend < 0.001). These positive trends remained among workers with both high- and low-level silica exposure. There was also a positive trend for ischemic heart disease among workers with low-level exposure, with quartile HRs of 1.04, 1.13, 1.52, and 1.60 (*P* for linear trend < 0.001).

Conclusion: Low-level crystalline silica exposure was associated with increased mortality from heart disease, including pulmonary heart disease and ischemic heart disease, whereas high-level exposure mainly increased mortality from pulmonary heart disease. Current permissible exposure limits for crystalline silica in many countries may be insufficient to protect people from deaths due to heart disease.

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From the [a]Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (Incubating), Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [b]Institute of Health Surveillance, Analysis and Protection, Hubei Center for Disease Control and Prevention, Wuhan, Hubei, China; [c]Department of Epidemiology and Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA; and [d]Department of Epidemiology, Harvard School of Public Health, Boston, MA.

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Correspondence: Weihong Chen, 13 Hangkong Road, Wuhan, Hubei 430030, China. E-mail: wchen@mails.tjmu.edu.cn.

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Crystalline silica is one of the most common minerals on earth. Environmental exposure to ambient crystalline silica can occur during natural, agricultural, or industrial activities. The natural resources mainly include volcanic explosions, windblown soils, and long-range transport during dust storms.[1,2] Volcanoes are a major source of natural silica, and 9% of the world's population lives within 100 km of historically active volcanos.[1] Agricultural crystalline silica exposures have been reported to be the result of working the soil and from harvesting certain types of crops.[3] The International Labor Organization estimated that 1.1 billion farm workers worldwide[4] may be potentially exposed to crystalline silica. Crystalline silica exposure is one of the most serious occupational hazards. The US Occupational Safety and Health Administration estimated that over 2 million US workers were exposed to silica dust in general industry, construction and maritime industries in 2003.[5] Recent reports estimated that there were 23 million silica-exposed workers in China,[6] over 3 million in India,[7] and over 2 million in Europe.[8] Crystalline silica has been linked with silicosis,[9] lung cancer,[10] and renal disease.[11] Its adverse health effects have drawn much public health concern worldwide.[11–13]

Several studies have been conducted to assess the association between crystalline silica exposure and mortality from heart disease, especially ischemic heart disease, but the evidence remains less clear.[14] Some studies reported increased ischemic heart disease mortality among silica-exposed persons,[15–18] but most of these studies were conducted based on standardized mortality ratio (SMR), which was estimated by comparing the study subjects with a general population. This may underestimate exposure-related risk because of the healthy worker effect.[19] Another problem is that most studies did not have sufficient data on silica exposure and on potential confounding factors such as smoking. Therefore, few exposure–response analyses have been conducted (which provide the strongest evidence for causality). In addition, few studies quantitatively reported the association between silica exposure and mortality from hypertensive heart disease and from pulmonary heart disease that can result from a respiratory disorder.

In the late 1980s, we established a cohort of 74,040 workers from 29 mines and pottery factories in China.[13,20]

A previous analysis showed a possible association between crystalline silica and heart disease mortality among the entire cohort.[13] Because detailed information on work history and/or lifestyle were not available for 43% of cohort participants, we did not adjust for any potential confounders and did not conduct detailed exposure–response analysis in the previous report. Here, we extend the analyses to examine the association among the remaining 42,572 participants, considering potential confounders for heart disease such as smoking, education, and drinking. Furthermore, we investigated the association between crystalline silica and heart disease mortality with stratification by lifetime highest silica exposure.

METHODS

Study Population

Details of study design and methods of the Chinese silica cohort have been described previously.[13,20] Briefly, the cohort was established in the late 1980s and included 74,040 workers who worked at 29 Chinese metal mines and pottery factories for 1 year or more between 1960 and 1974. The cohort was retrospectively followed to 1960 and prospectively followed to 2003. Demographic information, work history, cause of death, and information on living habits were collected by trained investigators. We used the facilities' occupational records to obtain work history, including all job titles, with the corresponding start and end dates. Smoking data were collected by questionnaire between 1986 and 2004. The smoking data included average number of cigarettes per day and corresponding start and end dates, taking into consideration changes in smoking intensity. Silicosis was classified as stage I, II, or III based on the national diagnostic criteria, which had an acceptable agreement with the International Labour Office standard.[13,21] We restricted this study to 42,572 workers after excluding 31,468 workers without detailed data on yearly work history and/or smoking.

Silica Exposure Assessment

We conducted quantitative exposure assessment in this study. Occupational dust monitoring data were used to create a job-exposure matrix that included facility-, job-, and year-specific crystalline silica concentrations.[13] By linking the job-exposure matrix and work history, we defined the lifetime highest silica exposure (mg/m^3) for each worker as the highest silica concentration among all job titles. Cumulative silica exposure for each worker (mg/m^3-years) was calculated as follows: cumulative silica exposure $= \sum_{i=1}^{n}(C_i \times T_i)$, where n = total number of job titles, C = silica concentration for the ith job title, T = working years for the ith job title.[13]

End Points

Trained local occupational physicians traced the vital status during the follow-up. Underlying causes of death (99% complete) were obtained from local hospital records, employment information, or oral reports from colleagues or next-of-kin.[13] The 10th version of the International Classification of Diseases (ICD-10) was used to classify the causes of death. We divided causes of deaths into those resulting from heart disease (ICD-10 codes: I00–I09, I11, I13, and I20–I51), pulmonary heart disease (I26, I27), ischemic heart disease (I20–I25), hypertensive heart disease (I11), and other heart disease (I00–I09, I13, I28–I51). We also investigated mortality from nonmalignant respiratory disease (J00–J99), including silicosis (J62), pneumonia (J12–J18), and chronic bronchitis (J41, J42).

Statistical Analysis

The Cox proportional hazards model was used to conduct quantitative exposure–response analysis for crystalline silica exposure in relation to mortality from heart disease and from respiratory disease. We used age instead of calendar time as the time variable to define risk sets.[22] Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated, with adjustment for possible confounding factors including sex, year of birth, and smoking. Cumulative silica exposure was divided into quartiles, with the cutpoints chosen based on the exposure distribution among silica-exposed subjects. Linear trend was tested by including cumulative silica exposure as a continuous variable in the model.

To evaluate whether the association between silica exposure and mortality from heart disease and respiratory disease was modified by silica exposure level, we dichotomized subjects by lifetime highest silica exposure with a cutpoint of $0.1\ mg/m^3$ (which is the current permissible exposure limit used in many countries). With incidence density sampling, we employed penalized spline models to investigate the potential nonlinear association.[23] If a linear association was suggested, we instead fitted Cox proportional hazards models with linear functions of silica exposure. To investigate the possible influence of the healthy worker survivor effect, as recommended by Arrighi et al,[24] we conducted supplemental analyses in which we introduced a 15-year lag, or restricted the cohort to those with at least 15 years since hire. Statistical analyses were conducted with S-Plus version 8.0 (Insightful Corp., Seattle, WA) and SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 presents selected cohort characteristics. The cohort included 42,572 workers, of whom 27,480 were ever exposed to silica dust. During an average of 35 years (1,472,287.5 person-years) follow-up, we identified 2846 deaths from heart disease, including 1528 from pulmonary heart disease, 496 from ischemic heart disease, 322 from hypertensive heart disease, and 500 from other heart disease. A total of 2636 workers died from respiratory disease. We identified 5871 silicosis cases, including 333 cases among participants with low-level silica exposure and 5538 with high-level exposure. As shown in Table 2, mortality rates increased monotonically with quartiles of cumulative silica exposure for total heart disease, pulmonary heart disease, and

TABLE 1. Selected Cohort Characteristics by Crystalline Silica Exposure Level

Characteristic	Entire Cohort (n = 42,572)	Lifetime Highest Crystalline Silica Exposure		
		Unexposed (n = 15,092)	≤0.1 mg/m^3 (n = 8,633)	>0.1 mg/m^3 (n = 18,847)
Men; no. (%)	36,168 (85)	10,725 (71)	8,233 (95)	17,210 (91)
Year of birth; no. (%)				
1900–1929	9,874 (23)	2,471 (16)	864 (10)	6,539 (35)
1930–1939	15,077 (35)	4,944 (33)	1,962 (23)	8,171 (43)
1940–1949	11,613 (27)	4,865 (32)	3,758 (43)	2,990 (16)
>1949	6,008 (14)	2,812 (19)	2,049 (24)	1,147 (6)
Duration of follow-up (years); mean (SD)	34.6 (9.8)	34.1 (10.2)	34.7 (7.6)	34.9 (10.5)
Smoking amount (pack-years); no. (%)				
Never-smokers	17,006 (40)	8,138 (54)	2,838 (33)	6,030 (32)
0.01–21.33	6,381 (15)	1,829 (12)	1,543 (18)	3,009 (16)
21.34–31.92	6,423 (15)	1,595 (11)	1,499 (17)	3,329 (18)
31.93–42.00	6,400 (15)	1,708 (11)	1,617 (19)	3,075 (16)
>42.00	6,362 (15)	1,822 (12)	1,136 (13)	3,404 (18)
Smoking amount for ever-smokers (pack-years); mean (SD)	32.9 (16.4)	32.9 (17.0)	32.0 (16.5)	33.4 (16.0)
Cumulative silica exposure (mg/m^3-years); mean (SD)	3.7 (4.2)	0	0.6 (0.4)	5.1 (4.5)
Cases of silicosis; no. (%)	5,871 (14)	0	333 (4)	5,538 (29)

TABLE 2. Mortality Rates of Heart Disease and Respiratory Disease by Quartile of Cumulative Silica Exposure

Cumulative Silica Exposure (Quartiles; mg/m^3-years)	No. Persons at Risk	No. Person-Years at Risk	Mortality Rate (per 100,000 Person-Years)					
				Subtype of Heart Disease				
			Total Heart Disease	Pulmonary Heart Disease	Ischemic Heart Disease	Hypertensive Heart Disease	Other Heart Disease	Respiratory Disease
Total	42,572	1,472,287.5	193.3	103.8	33.7	21.9	34.0	179.0
0	15,092	514,675.7	109.8	28.6	29.1	18.7	33.4	40.2
0.01–0.75	6,838	234,741.7	83.1	22.6	27.3	11.9	21.3	52.8
0.76–1.84	6,888	247,601.0	129.2	44.0	44.0	13.7	27.5	86.8
1.85–5.37	6,871	249,895.0	248.1	131.3	41.2	30.4	45.2	297.3
>5.37	6,883	225,374.1	508.5	395.3	31.1	39.0	43.0	597.7

respiratory disease. Mortality rates due to ischemic heart disease increased at the second quartile but decreased thereafter. The overall mortality rates of ischemic heart disease, hypertensive heart disease, and other heart disease were much lower than that of pulmonary heart disease.

With adjustment for sex, year of birth, type of facility, and smoking, the categorical analyses gave monotonic exposure–response trends between silica exposure and mortality from total heart disease, pulmonary heart disease, respiratory disease, and pneumonia (all $P_{trend} < 0.001$) among all cohort subjects (Table 3). The HRs for continuous cumulative silica exposure among persons with and without silicosis were 1.040 (95% CI = 1.027–1.052) and 1.023 (1.004–1.043), respectively. Although there was also an overall negative association for ischemic heart disease mortality, the HR of the second quartile increased to 1.41 (1.09–1.83), indicating that risk might increase at lower silica exposure. We did not find a positive association between silica exposure and mortality from hypertensive heart disease, other heart disease, or chronic bronchitis.

Table 4 shows the results of exposure–response analyses stratified by lifetime highest silica exposure with a cutpoint of 0.1 mg/m^3. Among workers with high-level silica exposure, positive exposure–response trends were found for mortality from total heart disease, pulmonary heart disease, respiratory disease, and pneumonia (all $P_{trend} < 0.05$); however, negative exposure–response trends were detected for ischemic heart disease mortality ($P_{trend} = 0.006$). Among workers with low-level silica, a positive trend for ischemic heart disease mortality was found, with HRs of 1.04 (0.63–1.72), 1.13 (0.68–1.90),

TABLE 3. Association Between Crystalline Silica Exposure and Mortality from Heart Disease and Respiratory Disease Among the Entire Cohort

	Unexposed		Quartile of Cumulative Silica Exposure[b]								
			1		2		3		4		
	No.	HR[a]	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	P_{trend}
Total heart disease	565	1.00	195	0.89 (0.75–1.05)	320	1.09 (0.95–1.25)	620	1.32 (1.17–1.49)	1,146	2.10 (1.88–2.35)	<0.001
Pulmonary heart disease	147	1.00	53	0.92 (0.67–1.26)	109	1.39 (1.08–1.79)	328	2.47 (2.01–3.03)	891	5.46 (4.52–6.61)	<0.001
Ischemic heart disease	150	1.00	64	1.02 (0.76–1.38)	109	1.41 (1.09–1.83)	103	1.03 (0.78–1.35)	70	0.70 (0.51–0.96)	0.002
Hypertensive heart disease	96	1.00	28	0.93 (0.60–1.43)	34	0.69 (0.47–1.04)	76	0.81 (0.59–1.11)	88	0.77 (0.57–1.05)	0.01
Other heart disease	172	1.00	50	0.78 (0.56–1.08)	68	0.79 (0.59–1.06)	113	0.82 (0.63–1.05)	97	0.60 (0.46–0.79)	<0.001
Respiratory disease	207	1.00	124	1.24 (0.99–1.55)	215	1.96 (1.61–2.37)	743	4.85 (4.10–5.74)	1,347	7.92 (6.72–9.35)	<0.001
Silicosis	0		21	1.00	78	4.30 (2.64–6.99)	459	21.70 (13.72–34.33)	973	47.75 (30.11–75.71)	<0.001
Pneumonia	37	1.00	18	1.10 (0.62–1.95)	37	1.56 (0.98–2.48)	110	2.56 (1.73–3.78)	114	2.14 (1.45–3.16)	<0.001
Chronic bronchitis	96	1.00	31	1.15 (0.76–1.74)	30	0.83 (0.55–1.27)	62	0.98 (0.70–1.38)	114	1.17 (0.87–1.58)	0.95

[a]Reference category.
[b]Defined as 0.01–0.75, 0.76–1.84, 1.85–5.37, and >5.37 mg/m^3-years according to exposure distribution among silica-exposed subjects.

1.52 (1.02–2.27), and 1.60 (1.07–2.40) (P_{trend} < 0.001) for quartiles of cumulative silica exposure; positive trends for mortality from total heart disease, pulmonary heart disease, and respiratory disease remained, but the overall strength of associations decreased.

Data on education were available for 85% of study subjects, on marital status for 81%, and on alcohol drinking for 70%. Further adjustment for these lifestyle factors slightly attenuated all exposure–response trends, but the positive trends remained (P_{trend} <0.05). When considering the healthy worker survivor effect, exposure lag slightly increased the HRs of heart disease mortality although without a consistent trend (ie, the quartile HRs for ischemic heart disease among subjects with low-level silica exposure were 1.38, 1.46, 1.71, and 1.29). Cohort restriction did not appear to modify the association (ie, the quartile HRs for ischemic heart disease among subjects with low-level silica exposure were 1.05, 1.11, 1.56, and 1.62).

Using penalized spline models, we investigated the nonlinear associations for mortality from heart disease and respiratory disease by silica exposure level (Figure). The associations between silica exposure and mortality from total heart disease (low-level silica exposure) and ischemic heart disease were suggested to be linear (P for linear trend < 0.05; P for nonlinear trend > 0.05), and so we fitted the models with linear functions of cumulative silica exposure. Overall, the results by penalized spline models showed similar exposure–response trends, though some (mortality from total heart disease and pulmonary heart disease, high-level silica exposure) flattened at high cumulative silica exposure.

DISCUSSION

In this cohort study of 42,572 workers with an average of 35 years follow-up, long-term silica exposure was related to an increased risk of mortality from total heart disease, pulmonary heart disease, and ischemic heart disease. High-level silica exposure mainly increased mortality from pulmonary heart disease, whereas low-level silica exposure (under the permissible exposure limit of crystalline silica currently used in many countries) was associated with increased risk of mortality from not only pulmonary heart disease but also ischemic heart disease.

Few studies have reported the quantitative association between silica exposure and pulmonary heart disease mortality. With adjustment for potential confounders, including smoking, our exposure–response analyses showed a clearly positive association (quartile HRs: 0.92, 1.39, 2.47, and 5.46). Pulmonary heart disease mortality accounted for 54% of deaths from heart disease in this study. Previous analysis of this cohort followed to 1989 estimated that rate ratios of pulmonary heart disease mortality for medium- and high-level silica exposure were 1.27 (95% CI = 1.0–1.6) and 1.93 (1.6–2.4), respectively. The estimated risk was lower than those in the current study, which might be due to the shorter follow-up period.[20] Similarly, Dong et al[25] conducted a retrospective

TABLE 4. Association Between Crystalline Silica Exposure and Mortality from Heart Disease and Respiratory Disease Stratified by Lifetime Highest Silica Exposure

	Unexposed		Quartile of Cumulative Silica Exposure								
			1		2		3		4		
	No.	HR	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	P_{trend}
						>0.1 mg/m³[a]					
Total heart disease	565	1.00	247	0.98 (0.84–1.14)	373	1.15 (1.00–1.32)	549	1.63 (1.43–1.85)	862	2.14 (1.89–2.41)	<0.001
Pulmonary heart disease	147	1.00	88	1.24 (0.95–1.63)	183	2.03 (1.61–2.55)	357	3.77 (3.06–4.65)	690	5.80 (4.75–7.07)	<0.001
Ischemic heart disease	150	1.00	70	1.18 (0.87–1.59)	74	1.05 (0.78–1.43)	61	0.90 (0.65–1.24)	43	0.61 (0.42–0.89)	0.006[b]
Respiratory disease	207	1.00	156	1.60 (1.29–1.99)	404	3.69 (3.07–4.43)	749	6.71 (5.63–7.99)	954	7.44 (6.24–8.87)	<0.001
Silicosis	0		59	1.00	230	6.31 (4.86–8.21)	521	15.17 (11.80–19.52)	686	19.30 (14.90–24.99)	<0.001
Pneumonia	37	1.00	30	1.42 (0.87–2.33)	72	2.49 (1.64–3.79)	81	2.74 (1.81–4.14)	75	1.91 (1.25–2.91)	0.002
Chronic bronchitis	96	1.00	24	0.82 (0.52–1.30)	32	0.84 (0.55–1.28)	61	1.16 (0.82–1.65)	85	1.15 (0.83–1.60)	0.83
						≤0.1 mg/m³[c]					
Total heart disease	565	1.00	57	1.13 (0.85–1.49)	45	1.12 (0.82–1.53)	73	1.26 (0.97–1.62)	75	1.34 (1.04–1.72)	0.001
Pulmonary heart disease	147	1.00	14	1.46 (0.83–2.58)	11	1.51 (0.80–2.86)	14	1.29 (0.72–2.29)	24	2.40 (1.51–3.83)	<0.001
Ischemic heart disease	150	1.00	18	1.04 (0.63–1.72)	17	1.13 (0.68–1.90)	32	1.52 (1.02–2.27)	31	1.60 (1.07–2.40)	<0.001
Respiratory disease	207	1.00	38	2.20 (1.55–3.14)	33	2.22 (1.51–3.28)	53	2.27 (1.64–3.13)	42	1.97 (1.39–2.81)	<0.001
Silicosis	0		8	1.00	4	0.43 (0.11–1.65)	10	1.12 (0.44–2.86)	13	1.60 (0.64–4.01)	0.04
Pneumonia	37	1.00	6	1.29 (0.54–3.10)	4	1.45 (0.50–4.18)	6	1.36 (0.56–3.34)	5	1.22 (0.46–3.24)	0.43
Chronic bronchitis	96	1.00	8	1.31 (0.62–2.76)	11	2.08 (1.07–4.01)	10	1.16 (0.58–2.30)	6	0.83 (0.35–1.94)	0.75

[a]Analyses only included subjects without silica exposure and those with a lifetime highest silica exposure >0.1 mg/m³. Quartiles of cumulative silica exposure were defined as 0.04–1.73, 1.74–3.80, 3.81–7.06, and >7.07 mg/m³-years according to exposure distribution among silica-exposed subjects.

[b]Indicates significantly negative linear trend.

[c]Analyses only included subjects without silica exposure and those with a lifetime highest silica exposure ≤0.1 mg/m³. Quartiles of cumulative silica exposure were defined as 0.01–0.33, 0.34–0.55, 0.56–0.87, and >0.87 mg/m³-years according to exposure distribution among silica-exposed subjects.

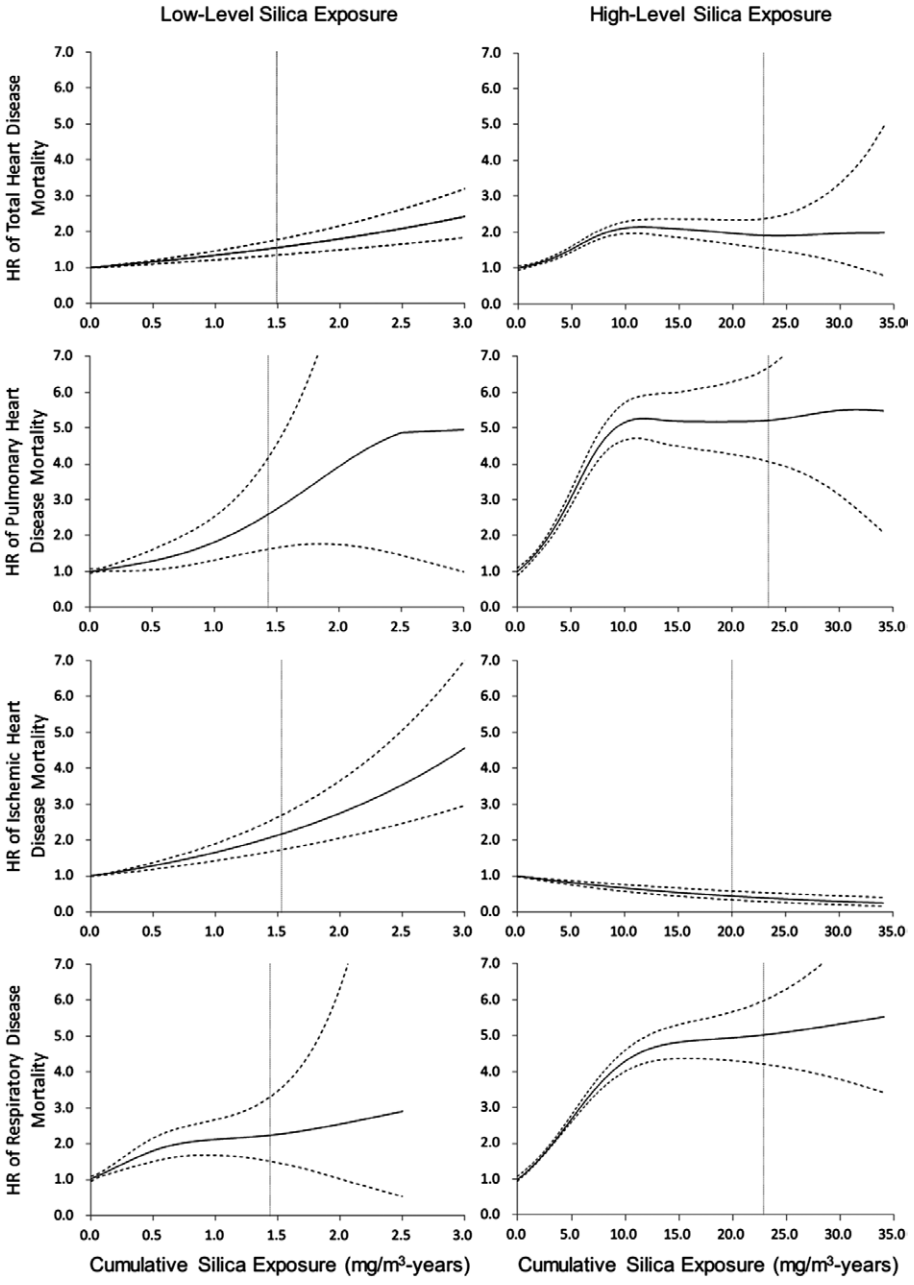

FIGURE. HRs (solid lines) and 95% CI (dashed lines) for heart disease and respiratory disease mortality associated with low- and high-level silica exposure by penalized spline models. The vertical dotted lines indicate the 95th percentile of cumulative silica exposure. "Low-level" exposure is lifetime highest silica exposure ≤0.1 mg/m^3 and "high-level" exposure is exposure >0.1 mg/m^3.

cohort study among 11,470 male steel workers exposed to silica dust and reported an increased standardized rate ratio (SRR) of 1.79 ($P < 0.01$) for pulmonary heart disease mortality. Silicosis is usually considered as a marker of high silica exposure[26] and may contribute to increased risk of pulmonary heart disease mortality. In a necropsy-based case–control study of 732 South African gold miners, both the presence and severity of silicosis were associated with the development of pulmonary heart disease.[27] Dong et al[25] reported that the SRR for pulmonary heart disease mortality among persons with silicosis (3.08) was remarkably higher than that among those without silicosis (0.74). We found similarly higher risk of pulmonary heart disease mortality among persons with silicosis (HR for continuous cumulative silica exposure = 1.040 [95% CI = 1.027–1.052]) compared with those without silicosis (1.023 [1.004–1.043]). Our results showed increased pulmonary heart disease mortality not only among workers with high silica exposure but also among those with low exposure, suggesting that silica exposure can increase pulmonary heart disease mortality independent of silicosis.

The association of ischemic heart disease mortality with crystalline silica exposure remains less clear. Wyndham et al[16] observed increased ischemic heart disease mortality (SMR = 1.15 [95% CI = 1.00–1.32]) among 3971 silica-exposed gold

miners; the effect on relative risk per 10 years of underground service was estimated to be 1.54 (1.04–2.28). However, this result could not be repeated in a case–control study within a cohort of 4925 gold miners.[28] According to our results, a worker with a 10-year silica exposure level of 0.1 mg/m^3 was estimated to have a 65% increased risk of ischemic heart disease death. In a cohort study of 4626 industrial sand workers highly exposed to crystalline silica, Steenland and Sanderson[15] reported an elevated ischemic heart disease mortality (1.22 [95% CI = 1.11–1.33]) compared with the US population. Recently, a Swedish cohort composed of 11,896 silica-exposed workers reported a SMR of 1.31 (95% CI = 1.24–1.38) for ischemic heart disease, suggesting a possible association.[18] In contrast, a cohort of 19,943 German construction workers with 10 years of follow-up reported a decreased ischemic heart disease mortality (SMR = 0.61 [95% CI = 0.50–0.74]).[29]

Our quantitative exposure–response analyses showed a positive association between silica exposure and ischemic heart disease mortality among workers with low-level exposure but a negative association among workers with high-level exposure. This may partially explain why previous studies obtained inconsistent results. The possible reason for decreased ischemic heart disease mortality among workers with high silica exposure is that more deaths resulted from the competing heart diseases, such as pulmonary heart disease. The presence of respiratory disease, especially silicosis, may increase the pulmonary heart disease risk. In our study, the overall prevalence and mortality rate of silicosis among workers with high silica exposure was 29% and 4%, respectively, which was much higher than those with lower silica exposure (4% and 0.2%). The biological mechanisms behind the positive association are not well explored. Previous studies suggested that silica-induced inflammation, improving resistance of pulmonary gas–blood exchange, and coagulation might play important roles.[18,30,31]

We did not use average silica exposure (cumulative silica exposure/duration of exposure) to stratify exposure level because such exposure does not represent exposure intensity (ie, a worker with short-term high silica exposure and long-term low silica exposure may produce similar cumulative silica exposure). Instead, we used lifetime highest silica exposure, which makes our result more practical for public health policy. The value of 0.1 mg/m^3 was selected because it has been used as the permissible exposure limit for silica in many countries, including the United States, Canada, France, and Italy. Previous studies have indicated the inadequacy of this standard in preventing silicosis, lung cancer, and renal disease.[10,32,33] Our study provided further evidence that long-term exposure to crystalline silica with concentrations under the permissible exposure limit could dramatically increase risk of heart disease mortality.

One of the strengths of this study is the large sample size (n = 42,572) and long period of follow-up (35 years), which provided adequate power for the analyses for subtypes of heart disease and stratified analyses; in particular, it enabled us to define the "real low" level of silica exposure according to the permissible exposure limit. Another feature of this study is that the crystalline silica exposure was quantitatively evaluated using detailed data on work history and workplace surveillance, which allowed us to conduct the quantitative exposure–response analyses. In addition, we collected detailed smoking data and thus were able to adjust for the potential confounding effect by smoking.

Our study has several limitations. One is that silica concentrations before 1950 were estimated using the concentrations in 1950, which might have led to underestimates of crystalline silica exposure for those who started work before 1950. Second, the smoking data for a few deceased subjects were obtained from their next-of-kin or colleagues, and recall bias might apply. Third, although we adjusted for several lifestyle factors (smoking, alcohol drinking, education, and marital status), there is still the potential for uncontrolled confounders, for example, by correlation between silica exposure and other health-conscious behaviors. However, known confounders had little influence on exposure–response trends. Finally, the healthy worker survivor effect might lead to underestimation for risk of heart disease mortality.

In this large cohort study with a considerably long period of follow-up, we found that long-term silica exposure was associated with increased risk of mortality from heart disease. For persons with low-level silica exposure, increased risks for both pulmonary heart disease and ischemic heart disease mortality were documented. Current regulatory standards for crystalline silica exposure in many countries may be insufficient to protect workers from deaths due to heart disease.

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