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List of terms and abbreviations

CI: confidence interval

NMRD: non-malignant respiratory disease (excludes pneumonia, influenza, and other infectious diseases)

HWSE: healthy worker survivor effect

MSHA: Mine Safety and Health Administration

OSHA: Occupational Safety and Health Administration

ACGIH: American Conference of Government and Industrial Hygienists

Evaluating impacts of occupational exposure limits for silica using g-estimation

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Abstract

Often, the harmful effect of an occupational exposure is difficult to detect in a standard analysis because workers who become ill leave employment sooner, which limits their cumulative exposure. Healthier workers remain employed longer, accumulating more exposure; this contrast makes the exposure appear neutral or beneficial. Using a method of analysis designed to address this issue, we estimated how many years of life were lost due to crystalline silica exposure in the diatomaceous earth industry in Lompoc, California, 1942-2011.

The cohort consisted of white men (Hispanic and non-Hispanic), because women and non-white workers in these facilities were too few to study in a meaningful statistical analysis. Workers in the diatomaceous earth industry are exposed to respirable crystalline silica, which is a known lung carcinogen and has also been linked to increased risk of non-malignant respiratory diseases. If workers who died of natural causes had never been exposed to crystalline silica, we estimated that half of them would have lived at least 0.48 (95%CI: 0.02, 1.01) years longer than they actually lived.

This estimate was considerably stronger for respiratory causes of death. Those who died of non-infectious non-malignant respiratory diseases (mainly chronic obstructive pulmonary disease) would have lived a median of 3.22 (0.82, 7.75) years longer under no exposure. Similarly, workers who died of lung cancer would have survived a median of 2.21 (0.97, 3.56) years longer in the absence of exposure.

These results confirm the known effects of crystalline silica exposure both on lung cancer and on non-malignant respiratory diseases, providing estimates of the numbers of years of life lost due to exposure, rather than estimates of increased risk. That is, we assumed these workers would have died of the same causes even if they had not been exposed to crystalline silica, and this analysis indicates that the exposure shortened their lives substantially.

Results for ischemic heart disease were inconsistent, but this may be because the effect of inhaled crystalline silica on this cause of death is smaller than its effect on diseases affecting the lungs, so a larger study population would be needed to obtain reliable results.

Completely eliminating exposure to crystalline silica in these workplaces would not be feasible. However, we also found evidence that limiting exposures to 0.025mg/m^3, as recommended by the American Conference of Government and Industrial Hygienists, might be nearly as effective for all-cause mortality and would substantially reduce the number of years of life lost due to crystalline silica among workers who die of lung cancer or non-malignant respiratory disease. Workplaces that intervene to comply with this Recommended Exposure Limit can potentially lengthen the lives of at least some of their employees by a significant amount.

Section 1

Significant or key findings

Often, the harmful effect of an occupational exposure is difficult to detect because workers who become ill leave employment sooner. Healthier workers remain longer, accumulating more exposure, so the exposure appears neutral or beneficial. Using a method of analysis designed to address this issue, we estimated how many years of life were lost due to crystalline silica exposure in the diatomaceous earth industry in Lompoc, California, 1942-2011.

If workers who died of natural causes had never been exposed to crystalline silica, half of them would have lived at least 0.48 (95%CI: 0.02, 1.01) years longer than they actually lived. Another way to quantify this estimate is that if everyone had been exposed to crystalline silica at an average daily intensity of 0.1mg/m^3 every year from entering the cohort to the end of follow-up, survival time from cohort entry would have been a median of 3% (0.1, 5.7) shorter than it would have been under no exposure. Note that for workers who died of natural causes that are not related to crystalline silica, eliminating exposure could not change their time of death, so the estimates for mortality from all natural causes will be lower than for causes of death that are related to crystalline silica exposure.

The estimates were indeed stronger for respiratory causes of death. Those who died of non-infectious non-malignant respiratory diseases (mainly chronic obstructive pulmonary disease) would have lived a median of 3.22 (0.82, 7.75) years longer under no exposure. Half of these workers would have died an estimated 10% (3.2, 16.3) sooner if they had always been exposed at an intensity of 0.1mg/m^3 than they would have if they had never been exposed.

Similarly, we estimated that half the workers who died of lung cancer would have survived at least 2.21 (0.97, 3.56) years longer in the absence of exposure. These workers would have died 9.8% (5.3, 14.1) sooner (median) if they had always been exposed at an intensity of 0.1mg/m^3 than if they had never been exposed.

These results confirm the known effects of crystalline silica exposure both on lung cancer and on non-malignant respiratory diseases, providing estimates of the numbers of years of life lost due to exposure rather than estimates of increased risk. Many other studies have only considered quartz, but the workers under study here were exposed to crystalline silica that was mostly in the form of cristobalite; the analyses reported here confirm that this form of silica is also deleterious to health.

Completely eliminating exposure to crystalline silica in these workplaces would not be feasible. However, we also found that limiting exposures to 0.025mg/m^3, as recommended by the American Conference of Government and Industrial Hygienists, might be nearly as effective for all-cause mortality and would substantially reduce the number of years of life lost due to crystalline silica among workers who die of lung cancer or non-malignant respiratory disease.

Translation of findings

While the Occupational Safety and Health Administration promulgated a new standard for silica with a Permissible Exposure Limit of 0.05mg/m^3 in 2016,(1) many silica-exposed workers are not under its jurisdiction. Mines are regulated under the Mine Safety and Health Administration (MSHA) instead. In 2010, MSHA acknowledged the need for an updated standard.(2) We conducted this study in hopes of helping to provide guidance for developing an updated standard.

Our main analysis estimated how much longer workers would have survived had they not been exposed to crystalline silica. However, Specific Aim 3 considered a series of other interventions based on limiting exposures to various levels. These analyses each assumed that exposure intensity did not matter, except for whether or not the annual average daily exposure intensity exceeded a given cutoff value. Results appeared stronger with this assumption.

For all-cause mortality, limiting crystalline silica exposure to the median observed intensity of 0.117mg/m^3 or to the OSHA standard of 0.05mg/m^3 appeared to offer moderate benefit to workers (1.5 [0.3, 2.7] or 1.9 [1.1, 3.2] years longer survival, respectively, compared to observed survival times), whereas the American Conference of Governmental and Industrial Hygienists' (ACGIH) recommended limit of 0.025mg/m^3 was estimated to be nearly as protective as completely eliminating the exposure (2.5 [1.6, 4.1] vs. 2.8 [1.3,5.5] years longer survival, respectively).

For workers who died of lung cancer, non-malignant respiratory diseases, or ischemic heart disease, eliminating the exposure was considerably better than any of the other limits, but we estimated that a limit of 0.025mg/m^3 would still have resulted in substantially longer survival: 12.0 years for lung cancer, 5.9 years for non-malignant respiratory diseases, and 2.9 years for ischemic heart disease.

Results have been disseminated in a poster at the conference of the International Society for Environmental Epidemiology in Rome, Italy in September of 2016, a presentation at the occupational epidemiology conference EpiCOH in Edinburgh, Scotland in August of 2017, and in an article in the open-access, peer-reviewed scientific journal *Environmental Epidemiology*.(3)

Based on these estimates, we recommend that workplaces not in compliance with the ACGIH recommendation should develop interventions to bring crystalline silica exposure intensities down to the recommended limit of 0.025mg/m^3, and even lower if possible.

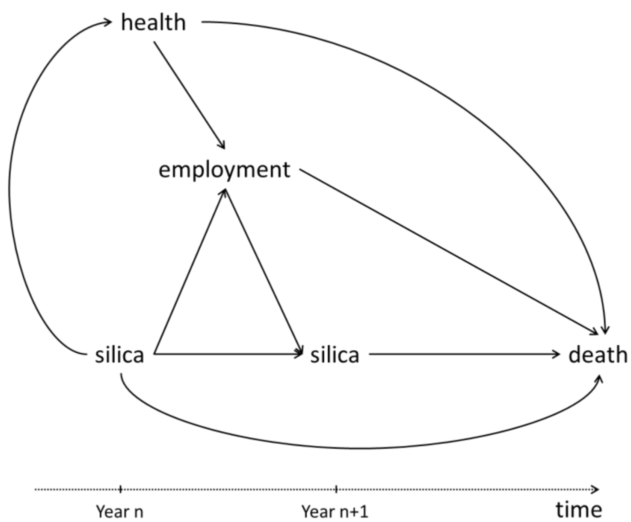
Research Outcomes/Impact (potential, intermediate, and/or end outcomes)

Because this was an analysis of existing data and not an intervention, no intermediate or end outcomes could be achieved. The potential outcomes are described above: if workplaces where employees are exposed to crystalline silica can limit such exposure to below 0.025mg/m^3, employees are likely to live substantially longer.

Section 2: Scientific report

Background: Inhaled crystalline silica in the workplace is a recognized lung carcinogen(4-7) that causes many other adverse outcomes. The earliest identified was silicosis, a progressive fibrotic form of pneumoconiosis.(6, 8, 9) Occupational exposure to crystalline silica also reduces lung function(10-12) and increases the risk of other non-malignant respiratory diseases, including chronic obstructive pulmonary disease.(7, 13, 14) A recent alarming increase in pneumoconiosis prevalence and severity among Appalachian coal miners has been attributed at least partially to silica exposure.(15, 16)

Quantifying the relation of silica exposure to outcomes other than silicosis is challenging. When occupational exposures adversely affect health, symptomatic workers may reduce their exposure by transferring to jobs with lower exposure or leaving employment entirely. The healthiest workers then accumulate the most exposure over time, giving rise to a paradoxical phenomenon called the healthy worker survivor effect (HWSE): higher cumulative exposure appears to be associated with longer survival and lower risk of the outcome.(17-19)



Traditional regressions yield biased results when prior exposure affects time-varying confounders, whether or not the confounders are included in the model.(20) The HWSE phenomenon is one example: health-related variables, even if unmeasured, may share causes with or directly affect the outcome and can also affect employment status, which in turn determines whether or not the worker continues to be exposed. Time-varying confounding by health and by employment status/duration is thus present, and it is hypothesized to be affected by prior exposure (see Figure). Therefore, correct adjustment for it requires special methods,(20) *e.g.*, g-estimation of a structural nested accelerated failure time model.(21, 22) The recent occupational epidemiology literature includes several applications of this method.(23-29)

The link between cumulative exposure to crystalline silica (including both quartz and cristobalite) and lung cancer was confirmed in 2001 in a pooled epidemiologic analysis of data from 10 studies,(5) including a cohort of workers in the diatomaceous earth industry.(30-32) Diatomaceous earth is the fossilized remains of certain algae whose cell walls are mostly amorphous silica; it also contains a small proportion of quartz. After extraction from a quarry mine, processing includes calcining at high temperatures, which increases the proportion of cristobalite.(30) Processed diatomaceous earth is used as a filtration material for liquids and as an insecticide.

Workers in the diatomaceous earth cohort were exposed to crystalline silica, principally cristobalite, and followed for mortality from various causes. In traditional analyses, risks of both lung cancer and non-malignant respiratory diseases increased with higher cumulative exposure.(7, 30-32) However, the strength of these associations may have been underestimated due to bias from HWSE. If so, regulations based on those findings may not be stringent enough to protect worker health. The Occupational Safety and Health Administration (OSHA) recently promulgated a new standard for silica with a Permissible Exposure Limit of 0.05mg/m^3,(1) but mines are regulated under the Mine Safety and Health Administration (MSHA) rather than OSHA. MSHA issued a statement in 2010 acknowledging that the industry standard, based on an assessment from 1973, is outdated.(2) Thus, more recent analyses may help in establishing a safer standard.

The cohort is described in detail in a prior publication.(30) Briefly, it includes 2342 white male workers from two diatomaceous earth mining and processing plants in Lompoc, California. Workers entered the cohort after employment for at least one year at either plant, including at least one day between 01/01/1942 and 31/12/1987. Work histories and silica exposure assessments were available from the beginning of plant operations (1902 and 1946 for the two plants) through 1994, with mortality follow-up from 01/01/1942 through 31/12/2011 based on National Death Index data, state driver's license bureaus, and commercial credit bureaus. Workers lost to follow-up (N=183) were censored the day after their last observed date of employment.

Industrial air monitoring measurements between 1962 and 1988 were used to estimate quantitative dust exposure, while data archived by the company provided information for the period 1948-1962.(33) Job-specific respirable dust exposure estimates were generated based on available measurements, and exposures before 1948 were extrapolated, accounting for changes over time.(32) Estimates for exposure to respirable crystalline silica were derived from the percent of silica contained in a given product and the exposure time to that product for each job.(32, 33) Job-specific exposure intensities (mg/m^3) were used to create the time-weighted average daily exposure intensity for each worker in each year, which was then lagged by 17 years to account for both the latency period for cancer and the unavailability of job history data after 1994. Prior work in this cohort suggests that a 10-year lag might be better for NMRD mortality,(34) but this would have reduced power, and we used the same lag in order to prioritize consistency between the two analyses.

Because two small operations in the plants involved chrysotile asbestos, asbestos exposures were derived from monitoring data and records of quantities of asbestos in mixed products from 1930 onwards. Exposures for earlier years were extrapolated.(32) Demographic information included hire year, duration of employment at study sites, dates of specific jobs held, and Latino ethnicity. Smoking status (ever/never, collected by the industry's medical surveillance program starting in the 1960s(30)) was available for 50% of the cohort (N=1171).

Separate analyses were conducted for mortality from all natural causes; lung cancer; NMRD excluding pneumonia, influenza and other infectious diseases; and ischemic heart disease. For ischemic heart disease we also ran analyses without the 17-year exposure lag.

Path analysis confirmed that time-varying confounding affected by prior exposure was present, so traditional regression would yield biased results. We therefore applied g-estimation of a structural accelerated failure time model to adjust for time-varying confounding as described below for each specific aim.

Specific Aims

1. Evaluate the dose-response relationship between exposure to silica dust and mortality from lung cancer, cardiovascular diseases, non-malignant respiratory diseases, and all causes combined (excluding external causes), using a method that adjusts correctly for healthy worker survivor effect. This method, g-estimation of an accelerated failure time model, assumes a log-linear effect of exposure on survival time.

Methodology: For each outcome, survival time is defined as the time from cohort entry to the date of death. We modeled counterfactual survival times that would have been observed under no exposure, starting from entry into the cohort, as a function of observed exposures and observed survival times, assuming a log-linear exposure-response in a structural nested accelerated failure time model:

$$T_{\bar{0}}(\psi) = \int_{0}^{T} \exp[\psi \times A(t)]\, dt$$

In this equation, T is observed survival time, $A(t)$ denotes observed exposure (mg/m^3) in year t, and ψ represents the unknown constant parameter of the model; when we use its true value, $T_{\bar{0}}(\psi)$ represents the counterfactual survival time under no exposure. We estimated ψ using g-estimation, which was developed by Robins(21) and is explained in pedagogical detail by Hernán et al.(22) This parameter can be interpreted as the negative log of the ratio of median survival times, comparing what would have happened if everyone had been exposed at an intensity of one unit every year of follow-up (regardless of employment status) to what would have happened if everyone had always remained unexposed. We subtracted this ratio from 1 to obtain the relative difference in median survival times, but these measures of etiologic effect are quantified with reference to an implausible scenario, as workers are not exposed to silica after leaving employment. We therefore used our estimate to calculate the median number of years of life that would have been saved per worker (compared to the observed scenario) under a ban on exposure to crystalline silica in the Lompoc plants, which has a more practical interpretation.(29)

For some more intuition on how this structural model works, note that if $\psi = 0$, then regardless of the exposure, $\exp[0 \times A(t)] = 1$, so the equation reduces to

$$T_{\overline{0}}(\psi) = \int_0^T 1dt = T - 0 = T$$

That is, if the true value of ψ is zero, then the counterfactual survival time if unexposed is the same as the observed survival time, regardless of exposure. In other words, exposure has no effect.

Likewise, for workers who were never exposed, $A(t) = 0$, and the calculation will work out the same way. No matter what the true value of ψ is, workers who were never exposed have a counterfactual survival time if unexposed that is equal to their observed survival time.

The equation holds true if we replace the observed quantities by what would happen under a counterfactual exposure scenario, too.(22) Counterfactual exposure history is denoted $\overline{a}(t)$, and the counterfactual survival time is $T_{\overline{a}}$:

$$T_{\overline{0}}(\psi) = \int_0^{T_{\overline{a}}} \exp[\psi \times a(t)]\, dt$$

If workers were exposed every year at an intensity of one unit, then the counterfactual exposure $a(t) = 1$ for all t and we denote the counterfactual always-exposed survival time by $T_{\overline{1}}$. In that case,

$$\begin{aligned} T_{\overline{0}}(\psi) &= \int_0^{T_{\overline{a}}} \exp[\psi \times a(t)]\, dt \\ &= \int_0^{T_{\overline{1}}} \exp[\psi \times 1]\, dt \\ &= T_{\overline{1}} \exp[\psi]. \end{aligned}$$

Thus, solving for the parameter, we find that $\psi = -\ln\left[\frac{T_{\overline{1}}}{T_{\overline{0}}}\right]$: the parameter equals the negative log of the ratio of (median) survival times comparing everyone always exposed at an intensity of one unit to everyone never exposed.

In our application, time is measured in years (other than the possible fractions of years at the very beginning and very end of a worker's time on follow-up), so this integral is actually a discrete sum. In each year, a worker could be unexposed (in which case that year contributes $\exp[0] = 1$ to the sum) or exposed (in which case that year contributes $\exp[\psi \times A(t)]$ to the sum). If exposure is harmful, then being unexposed results in longer survival time (*i.e.*, $T_{\overline{0}}(\psi) > T$ for workers who were ever exposed), which is equivalent to $\psi > 0$. If being exposed is beneficial (as in the case of medications), then $T_{\overline{0}}(\psi) < T$ for workers who were ever exposed (i.e. they were observed to live longer than they would have lived if they had not been exposed), which implies that $\exp[\psi \times A(t)] \leq 1$, so $\psi < 0$.

Combining exposure over time into cumulative exposure would conflate the possibly different effects of intensity and duration of exposure.(35) This model takes into account a worker's entire quantitative history of exposure to silica (that is, $A(t)$ at each time t) without summarizing it in a single number (cumulative exposure= $\int_{t=0}^{T} A(t)dt$).

G-estimation leverages the assumption that there are no unmeasured confounders of the exposure-outcome relation, or, equivalently, that counterfactual outcomes are statistically independent of observed exposures, conditional on measured covariates. This assumption implies that if we knew the counterfactual survival times, we could include them (or any function of them) along with all measured covariates in a model predicting observed exposures, and the coefficient of the counterfactual survival times would be 0. Our g-estimation procedure entailed choosing "candidate" values (within a reasonable search interval) for the unknown parameter ψ in the structural model and using them to calculate corresponding values $T_{\bar{0}}(\psi)$ for the counterfactual unexposed survival times from the structural model, observed exposures, and observed outcome times. Then, for each value of ψ, we tested whether the candidate counterfactual survival times were conditionally independent of observed exposures. Our estimate is the value of ψ that makes $T_{\bar{0}}(\psi)$ have coefficient equal to zero in a traditional multivariate regression predicting exposure $A(t)$. We predicted the level of exposure in categories defined by quartiles of the observed distribution, using ordinal logistic regression adjusted for the measured confounders: Latino ethnicity, smoking (ever/never/missing), age, calendar year, time taken off work in the previous year, exposure to silica in the previous year, previous cumulative exposures to dust and asbestos, and employment duration prior to start of follow-up.(22)

Not all workers died during follow-up; the analysis adjusted for administrative censoring by end of follow-up.(21) Those who survived to the administrative end of follow-up do not have an observed survival time, so we could not calculate a candidate counterfactual unexposed survival time. Furthermore, such survival may depend on exposure, so simply excluding those workers still alive from the analysis while including all those who died during follow-up would cause bias.(22) In order to adjust for this, we did not use $T_{\bar{0}}(\psi)$ itself directly in the exposure model. Instead, we used the following function of $T_{\bar{0}}(\psi)$:

$$\Delta(T_{\bar{0}}(\psi), C) = \begin{cases} \min[T_{\bar{0}}(\psi), C]\,, \text{if } \psi \geq 0 \\ \min[T_{\bar{0}}(\psi), C\ \exp(\psi\ A)]\,, \text{if } \psi < 0 \end{cases}$$

(where C represents the time from that worker's entry into the cohort to the administrative end of follow-up [*i.e.*, their maximum observable survival time] and A denotes the maximum observed exposure among all of the person-years included).(21) That is, if the candidate value for ψ was greater than 0, corresponding to exposure being harmful, we used $T_{\bar{0}}(\psi)$ only if a worker's outcome under no exposure would have occurred before the administrative end of follow-up, and otherwise used the total time the worker would have been observed during follow-up if unexposed. For further details, see Robins et al.(21)

This method of adjustment for administrative censoring results in a smooth estimating function, and the local slope is used to estimate confidence intervals.(24, 36)

All analyses were adjusted for censoring by loss to follow-up by applying inverse probability of censoring weights (estimated based on Latino ethnicity, age, calendar year, smoking, cumulative prior exposures to silica, dust, and asbestos, and employment duration prior to cohort entry), in order to assess what would have been observed in the absence of loss to follow-up.

Results: For mortality from all natural causes, if everyone had been exposed to crystalline silica at an average daily intensity of 0.1mg/m^3 (approximately the 32nd percentile of nonzero exposures), every year from entering the cohort to the end of follow-up, survival time from cohort entry would have been at least 3.0% (95%CI: 0.1,5.7) shorter for half the workers than it would have been under no exposure. The corresponding estimate for lung cancer from analysis without weights for competing risks (9.8% [5.3,14.1]) was stronger than that for all natural causes. The estimate for NMRD was 1.6% (-6.6, 9.2).

We estimated that half the workers who died of natural causes during follow-up would have lived at least 0.48 (0.02,1.01) years longer than they actually did, if they had never been exposed to crystalline silica. Half the workers who died of lung cancer would have lived at least 2.21 (0.97, 3.56) years longer, and half of those who died of NMRD would have lived at least 0.40 (-1.16,2.90) years longer than they actually did, if they had never been exposed to crystalline silica.

Results for analyses of ischemic heart disease were inconclusive and depended on the lag. With a 17-year lag, results appeared null; with no lag, analysis rejected the null hypothesis but did not produce an estimate within the search interval of plausible values for the parameter.

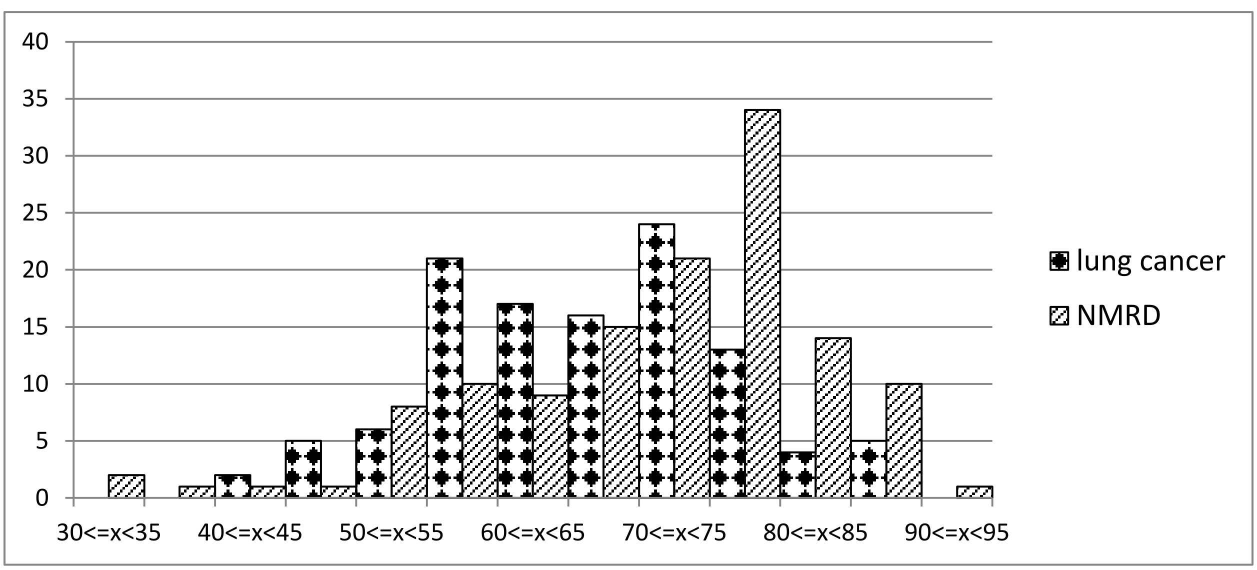
2. Again using the method from Aim 1, adjust the analysis for each outcome for competing risks. Evaluate the degree of bias that results from workers dying of causes other than the one of primary interest.

Methodology: Analyses were then conducted as described above, but with further weights to adjust for censoring by competing risks. For all natural mortality, the only potential competing risks are external causes of death; for lung cancer mortality, we considered death from NMRD a competing risk, and vice versa, because these two outcomes share many causes and are known to be related to silica exposure. The weights were equal to the inverse of the probability of remaining uncensored (i.e., not being lost to follow-up, and not dying from specific competing risks: the product of the estimated probabilities) from that time forward.(22) These probabilities were predicted on the basis of Latino ethnicity, age, calendar year, smoking, cumulative prior exposures to silica, dust, and asbestos, and employment duration prior to cohort entry.

Results: Estimates from the analysis of mortality from natural causes were not sensitive to adjustment for censoring by deaths from external causes; with this adjustment we estimated that workers would have lived a median of 0.49 (0.03, 1.02) years longer if they had never been exposed to crystalline silica. This is consistent with the plausible assumption that mortality from external causes either does not share risk factors with mortality from natural causes or is not associated with exposure. For natural-cause mortality, then, non-adjustment for censoring by deaths from external causes did not introduce bias.

In the analysis of NMRD mortality, when we adjusted for censoring by death from lung cancer, we estimated that half the workers would have died 10% (3.2, 16.3) sooner if they had always been exposed at 0.1mg/m^3 than they would have under no exposure. The median estimated number of years of life that would have been saved among workers who died of NMRD if they had never been exposed to crystalline silica (compared to their observed survival times under the exposures they actually experienced) was 3.22 (0.82, 7.75). This means that a substantial bias of -88% was introduced by not adjusting for censoring by death from lung cancer.

For lung cancer mortality, adjusting for censoring by death from NMRD did not produce an estimate at all: the estimating function did not cross 0 in the search interval, though the analysis did reject the null hypothesis. However, the age distributions at death from the two causes were very different (see Figure below). In particular, deaths from lung cancer tended to occur at younger ages than deaths from NMRD, making it much more likely that lung cancer mortality acted as a competing risk for NMRD than vice versa.



Thus, although we could not quantify the bias introduced by not adjusting for censoring due to deaths from non-malignant respiratory diseases in our analysis of the relationship between silica exposure and lung cancer mortality, we do not believe it was substantial.

3. Address the questions from a public health perspective by evaluating the effects of hypothetical interventions to limit exposure to silica.

    a. For each cause of death, calculate the life-years that could have been saved under a series of different hypothetical exposure limits for silica, using g-estimation of an accelerated failure time model with a series of binary exposure variables.

Methodology: We repeated analyses from the previous Aims, replacing the quantitative exposure metric with each of a series of binary exposure metrics defined by silica concentrations above vs. below cutoffs(28) corresponding to the median observed annual average daily exposure (0.117mg/m^3), the OSHA standard (0.05mg/m^3),(1) the American Conference of Governmental and Industrial Hygienists' recommended limit (0.025mg/m^3),(37) and a ban (0mg/m^3).

An analysis using a binary exposure metric indicating whether a worker was ever exposed at all in that year (*i.e.*, a cutoff of 0mg/m^3) theoretically asks the same question asked in the main analysis: what would have happened if no one were ever exposed to silica? However, the assumptions made in specifying the models in the two analyses are different. In the analyses for Specific Aims 1 and 2, exposure intensity is assumed (if held constant over time) to have a log-linear effect on survival time; in the analysis for Specific Aim 3, exposure intensity is assumed to have no importance whatsoever, with exposure duration having a log-linear effect on survival time.

For NMRD, we adjusted for censoring by lung cancer death, since our work on Specific Aims 1 and 2 implied that substantial bias would result otherwise: lung cancer death was an important censoring event. For the other outcomes we did not adjust for censoring by competing risks.

The estimating function for the g-estimation procedure used with the binary exposure metrics was not very well-behaved, so that variance estimation could only be done by running bootstraps. Due to the comparatively small numbers of cases for cause-specific mortality, many of the bootstrap samples did not yield estimates, so we were unable to estimate confidence intervals for specific causes of death.

Results: Estimates from these analyses were larger than those from Specific Aims 1 and 2. The median numbers of years of life that would have been saved per worker who died of the specified causes, under various exposure limits, are presented in the following Table, with confidence intervals for mortality from all natural causes.

Hypothetical exposure limit	Median years of life lost due to *all natural causes*	Median years of life lost due to *nonmalignant respiratory diseases*	Median years of life lost due to *lung cancer*	Median years of life lost due to *ischemic heart disease*
0 mg/m^3	2.8 (1.3,5.5)	6.7	17.1	6.9
0.025 mg/m^3	2.5 (1.6,4.1)	5.9	12.0	2.9
0.05 mg/m^3	1.9 (1.1,3.2)	5.6	10.3	2.6
0.117 mg/m^3	1.5 (0.3,2.7)	5.2	7.6	2.2

b. For each cause of death, calculate the potential reduction in risk under a series of different hypothetical exposure limits for silica, using g-estimation of a cumulative failure time model with a series of binary exposure variables.

Methodology: We explored this sub-aim but could not complete it. Application of the cumulative failure time model was too complicated in a situation in which different workers enter the cohort at different times, leading to dramatically different lengths of follow-up. There would be a major loss of statistical power if we limited follow-up to a comparatively short period that most workers attained, whereas attempting to estimate risk during follow-up longer than a worker's observed follow-up would require very ambitious extrapolation, which did not seem either wise or feasible using this model.

Discussion: Previous analyses applying traditional methods (including both regressions and standardized mortality ratios comparing rates in workers to those in the general population) have found reasonably consistent associations between exposure to silica and lung function,(10-12) as well as rates or risks of both lung cancer(5-7) and NMRD.(7-9, 13, 14) With survival time as the metric, our analysis does not allow direct quantitative inference about the effect of silica exposure on cause-specific mortality risks, because the model assumes that those who died of NMRD or lung cancer would have died of those causes even if they had not been exposed to silica. (This assumption is false for silicosis as a single outcome; our composite NMRD outcome includes chronic obstructive pulmonary disease and pneumoconiosis mortality.) Among workers for whom smoking was measured, only 2 lung cancer deaths and 5 NMRD deaths occurred in nonsmokers. Most of the cases would have therefore had elevated risks for these outcomes even without exposure to silica, making the assumption reasonably plausible. Controlling bias from the HWSE and assuming these workers would have died of the same causes even if they had not been exposed, we found that silica exposure was associated with *earlier* death—a new finding distinct from previously reported increased risks. However, these data cannot distinguish between earlier onset and more aggressive forms of the disease. Exposure to silica had a stronger, though less precise, relationship with NMRD than with lung cancer. The Aim 3 analyses using binary exposure metrics suggested that setting an exposure limit at 0.025mg/m^3 would have saved nearly as many years of life overall as a complete ban in this cohort, though this was less true for specific causes of death.

Results for ischemic heart disease were inconclusive. There may truly be an effect, as suggested by results from Aim 3 with exposure considered as a binary variable and by the rejection of the null hypothesis in the analysis with unlagged exposure in Aim 1, or there may not, as suggested by the results from Aim 1 with exposure lagged by 17 years. We suspect, however, that a lag of 17 years is not appropriate for this outcome. Analysis of a larger cohort, or using a different method, might be able to reach clearer conclusions for ischemic heart disease mortality.

For the other outcomes, we presented estimates of relative differences of median survival times comparing two hypothetical interventions (exposing everyone to crystalline silica at an average daily intensity of 0.1mg/m^3 in every year vs. never exposing anyone). Since workers are never exposed after they leave work, this estimate is not what would be observed under any feasible intervention. Nevertheless, it is informative in its own right as an estimate of the *etiologic* effect of a static intervention,(38, 39) and it resembles the type of measurement used by OSHA in setting standards (*i.e.*, estimated mortality following continuous exposure at a given level for 40 years). We also presented estimates of the median number of years of life that were lost due to exposure to silica, *i.e.*, estimates of the effect of an intervention that, while perhaps still not feasible, is meaningful from the *regulatory* point of view. These estimates compare what would have happened if silica exposure had been banned to what actually happened. This effect measure depends not only on the magnitude of the etiologic effect but also on the distribution of exposure among those who died of the cause of interest. Thus, even if the etiologic effect of silica exposure (*i.e.*, the true value of $\exp[\psi]$) were the same in another population of similar workers, the number of years of life lost due to silica exposure would be different if the population had a different exposure distribution.

An advantage of analyzing mortality from all natural causes is that, regardless of exposure, everyone will eventually experience the outcome (unless they first die from external causes), so the assumption that the accelerated failure time model requires is met. We found that workers would have lived about a half-year longer (median) if they had never been exposed to silica. This finding is presumably driven mostly by diseases already linked to silica exposure; indeed, the estimates for lung cancer and NMRD were stronger.

Lung cancer and non-malignant respiratory disease share their most important risk factors, so we expected each to act as an informative censoring event in the analysis of the other. Each of the two cause-specific analyses was sensitive to adjustment for competing deaths from the other cause using inverse probability of censoring weights. The unweighted estimate for NMRD was essentially null, even though the weighted estimate was strong. These results are consistent with lung cancer death acting as an informative censoring event in the analysis of NMRD: without adjustment for competing risks, the association between exposure to silica and NMRD mortality is difficult to detect.

By contrast, the analysis of lung cancer did not yield an estimate when weighting to adjust for censoring by NMRD death, though the unweighted estimate was convincing. The lung cancer deaths generally occurred at younger ages than deaths from NMRD, perhaps indicating that the people at risk of lung cancer did not live long enough for NMRD to progress to death. In that case, NMRD mortality did not act as a competing event for lung cancer mortality, whereas lung cancer deaths could censor deaths from NMRD, which were more likely to occur later in life.

Estimates from analyses without inverse probability of censoring weights for competing risks are easier to interpret; weighting the analysis is equivalent to estimating the effect in a pseudo-population in which death from the competing event cannot occur. Although preventing all deaths from lung cancer is unrealistic, the NMRD mortality analysis in a pseudo-population in which lung cancer mortality does not occur allows us to estimate the direct effect of exposure when the pathway of disease prevention via premature death is not included. Our results suggest that the impact of censoring by lung cancer death should be considered in analyses of NMRD mortality.

An application of the parametric g-formula to estimate subdistribution functions of risks in this cohort found qualitatively similar results, with silica linked more strongly to risk of NMRD mortality than lung cancer.(40) Our substantive conclusions (linking silica exposure to shorter survival times from both causes) are thus robust to different modeling assumptions and effect measures, lending further confidence to both results.

Our results were somewhat sensitive to the exposure metric used in the specification of the structural model. The Aim 3 analyses, with binary exposure metrics, yielded larger estimates; the reasons for this are unclear. One possible explanation is that the main results are underestimated due to violations of parametric assumptions (if, for example, the relation with survival time is not log-linear). Another possibility is that the relevant exposure is misclassified by the binary cutoffs.

Conditional exchangeability is the explicit basis for g-estimation.(22) The idea is that within strata of confounders, the exposure can be thought of as “randomized”—so differences in outcomes can be attributed to the exposure rather than to unmeasured differences between exposure groups. If an important confounder was unmeasured or excluded in the exposure model, then results would be biased. In this study, only crude smoking information was available and only for half the cohort, so there may be residual confounding by smoking or bias due to using a “missing” category in the analysis.(41) Exposures tended to be higher among those for whom the information was missing, but this was mainly because these were employees who left employment earlier during follow-up, when exposure levels were higher. If workers diagnosed with silicosis were more likely to quit smoking, then smoking status or intensity at time t might be affected by prior exposure. Detailed smoking data were unavailable,(30) but ever-smoking is not a strong predictor of exposure. Among workers whose smoking data were available, exposure levels while employed were similar for ever-smokers and nonsmokers. Results from other analyses in this cohort did not change much when multiple imputation was used to fill in missing smoking data, compared to using ever/never/missing categories.(40) Thus, as in many occupational studies, even though smoking is the most important risk factor for the outcomes under study here, its association with exposure is probably too weak to make it a strong confounder.(42-44)

One limitation of this analysis is that, because of the 17-year lag, we consider an intervention on exposure beginning in 1925, but follow-up begins in 1942; workers are only included if some of their employment occurred after the beginning of 1942. We cannot know if some excluded workers, who left employment before the start of follow-up, would have remained employed long enough under the intervention considered to be included in the cohort. Our results only apply to the workers included, who may be less susceptible than the excluded workers to the health effects of exposure to silica. However, in that case our results would be biased downward; the true effect might be slightly stronger in a cohort that includes all the workers. Only about 10% of our cohort had been employed for more than a year prior to the start of follow-up, though these workers accounted for 16% of natural cause mortality and lung cancer mortality, and 24% of NMRD mortality.

Conclusions: While it has been known for some time that workplace silica exposure increases the *risks* of diseases that shorten life, our results quantify the *number* of years of life lost due to exposure to crystalline silica. Applying a method that controls bias due to the HWSE, we estimated that survival times would have been significantly longer under a hypothetical intervention banning exposure, and that limiting exposures to 0.025mg/m^3 might still be quite effective for these workers. Given that MSHA has recognized the need to re-evaluate industry standards for crystalline silica,(2) this analysis and additional research should help guide policy.

Publications

Picciotto S, Neophytou AM, Brown DM, Checkoway H, Eisen EA, Costello S. Occupational silica exposure and mortality from lung cancer and nonmalignant respiratory disease: G-estimation of structural nested accelerated failure time models. Environmental Epidemiology. 2018;2(3):e029.

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