Association between Silica Exposure and Cardiovascular Disease Mortality: A Meta-Analysis

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Abstract

Background: Silica exposure is detrimental to health and has, thus, been a global health concern. We performed a systematic review and meta-analysis of existing articles to assess the involvement of silica exposure in cardiovascular disease (CVD) mortality.

Methods: Electronic databases including Web of Sciences, Scopus, PubMed, and Google Scholar were searched for eligible publication until December 2019. The pooled standard mortality ratio (SMR) and the 95% confidence interval (CI) were used to detect the association between silica exposure and CVD mortality.

Results: The pooled estimates of SMR indicated a nonsignificant association between silica exposure and CVD mortality (SMR: 1.26; 95% CI: 0.88-1.63). The subgroup analysis based on the type of CVD indicated a significant positive association between silica exposure and mortality from hypertensive heart disease (SMR: 2.45; 95% CI: 2.16 -2.74) and pulmonary heart disease (SMR: 4.03; 95% CI: 3.87-4.20).

Conclusion: This study confirmed that silica exposure is associated with an enhanced risk of mortality of hypertensive and pulmonary heart diseases. The verification of these results may have important effects on basic preventive strategies for health-care providers. Because of the mismatch in the silica exposure classification, some works in the literature were excluded. Also, the years of silica exposure may be important in CVD mortality. We suggest that these potential confounders be considered in future research.

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Introduction

Cardiovascular disease (CVD) is the result of complicated interactions between diverse risk factors, which can be modified.¹ The high number of CVD instances can be assigned to adjustable risk factors, so they should be regarded as preventable.² Despite significant progress in the prevention, diagnosis, and treatment of CVD, it is still the major cause of death in the world.³ Unfortunately, CVD prevalence is more common in low-income and middle-
environmental exposure to crystalline silica widely occurs in working and living environments. Different industries such as glass, ceramic, concrete, and electronics, as well as mining and agriculture, are sources of occupational silica exposure. Volcanic explosions, windblown soils, and dust storms are the natural sources of crystalline silica. Generally, exposure to crystalline silica is one of the most critical occupational risks. Strong epidemiologic evidence confirms the association between occupational silica exposure and different diseases such as silicosis, lung cancer, pulmonary tuberculosis, chronic obstructive pulmonary disease, rheumatoid arthritis, and renal disease.

In recent years, studies have focused more on the influence of environmental factors on the incidence of CVD. Exposure to environmental pollutants has a significant function in the development and severity of CVD. Various investigations have evaluated the association between silica exposure and mortality from CVD, but the result is not clear.

Using the method of evidence-based medicine to assess standard associated manuscripts, we performed the present systematic review and meta-analysis in order to confirm the involvement of silica exposure in CVD mortality.

### Methods

**Data Sources and Search Strategy**

In the current investigation, the quality of results was ensured via adherence to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A systematic search was performed to identify qualified studies published in comprehensive electronic databases, including Web of Sciences, Scopus, PubMed, and Google Scholar, until December 2019.

The search strategy was based on the following keywords: "ischemic heart disease" OR "ischaemic heart disease" OR "coronary artery disease" OR "myocardial infarction" OR "angina pectoris" OR "sudden cardiac death" OR "coronary death" OR "cardiovascular disease" AND "silicon-dioxide" OR "silicosis" OR "silica" OR "silicotics" OR "quartz". Additionally, the reference list of each manuscript was recovered, and articles were manually searched to recognize further acceptable studies. The filters employed were humans and the English language. (The search syntax for PubMed is shown in Supplement 1.)

**Inclusion and Exclusion Criteria**

Cross-sectional, case-control, and cohort studies were searched only in the English language. Documents on occupational silica exposure and CVD mortality were identified. Case reports, case series, letters to editors, review articles, animal studies, and conference records were excluded from the study.

**Data Collection**

Acceptability assessment and data abstraction were independently evaluated by 2 researchers (EM and KS). Any discrepancy in either stage was adjudicated by agreement. Data collection faults were reduced via data extraction using an extraction form. The data extracted were comprised of title, first author, country, study design, publication year, sample size, age (mean or range), number of events, and exposure type. The SMR values were extracted for the meta-analysis.

**Quality Assessment**

For the quality assessment of the articles, the improved Newcastle–Ottawa Scale (NOS) was used, and any discrepancy was adjudicated by agreement. This scale has 3 sections: selections (0–4 points), comparability (0–2 points), and exposure ascertainment (0–3 points), and the scores range from 0 to 9. The 2 researchers performed quality assessments independently. The scores of the studies were regarded as low-quality (< 7 points) and high-quality (≥ 7).

**Statistical Analysis**

The pooled SMR and the 95% confidence interval (CI) were summarized from the qualified studies using the random effect model. The heterogeneity between the studies was evaluated via the χ² test and I² statistics. In this research, I² of less than 25 denotes low heterogeneity, I² of 25% to 50% moderate heterogeneity, and I² of greater than 50% high heterogeneity. Publication bias was assessed via the visual evaluation of the asymmetry of the funnel plot and the statistical assessment through the Begg and Egger tests.

**Results**

**Literature Search**

Figure 1 displays the selection process for identifying eligible articles for the systematic review and meta-analysis of the association between occupational silica exposure and CVD mortality. A total of 973 studies were found at the initial stage of our research on the referred databases until December 2019. From this total, 193 duplicate articles and 151 irrelevant topics (through screening titles and abstracts) were excluded. In the full-text assessment, 140 articles were excluded because they were in languages other than English, letters, or reviews. Four articles were excluded because their...
estimation was based on hazard ratios. Finally, 7 cohort studies whose estimation was based on SMR remained for the final analysis.

**Study Characteristics**

The characteristics of the 7 selected studies are depicted in Table 1. The studies were performed on an extensive range of industries and occupations, including mining, pottery, and factory work. CVD mortality was evaluated in 4 studies, ischemic heart disease in 4 studies, and hypertensive and pulmonary heart diseases in 1 study. The sample sizes ranged from 213 to 74,040 workers. The duration of follow-up varied from 16 years to 47 years.

**Main Analysis**

The association between silica exposure and CVD mortality is illustrated in Figure 2. The pooled estimates of SMR showed a nonsignificant association between silica exposure and mortality due to CVD (SMR: 1.26 and 95% CI: 0.88 to 1.63). There was a high degree of heterogeneity between the results of the selected studies ($I^2$: 98.9% and $P < 0.001$).

**Subgroup Analysis**

The subgroup analyses were conducted based on the CVD type (Figure 3). A significant positive association was found between silica exposure and mortality from hypertensive heart disease (SMR: 2.45 and 95% CI: 2.16 to 2.74) and pulmonary heart disease (SMR: 4.03 and 95% CI: 3.87 to 4.20).

**Publication Bias Test**

According to the Egger test (t-value = 3.86 and $P = 0.003$), there was evidence of significant publication bias in the collected publications.

**Quality Assessment**

Three of the included studies in the present meta-analysis were low-quality, and the others were high-quality according to the NOS Scale (Supplement 2).

**Discussion**

The present meta-analysis is, to our knowledge, the first to evaluate the association between occupational silica...
exposure and the risk of CVD mortality in different workers. Our results indicated that occupational silica exposure was strongly associated with mortality due to hypertensive and pulmonary heart diseases. The risk of mortality owing to ischemic heart disease was slightly increased, but it failed to constitute statistical significance.

Hypertension is a major risk factor for CVD mortality; its prevention can, therefore, lessen the cardiovascular burden. Inflammation is involved in the development of hypertension via arterial stiffness. A growing body of evidence indicates that oxidative stress and inflammation are the major mechanisms for hypertension development. Silica dust can produce reactive oxygen species and increase oxidative stress. The production of inflammatory cytokines, reactive

### Table 1. Main characteristics of the included retrospective cohort studies

| First Author, Year | Country  | Sample  | Duration of Follow-up (y) | Characteristics | Events | SMR (95% CI) | Exposure                  | Quality  |
|-------------------|----------|---------|---------------------------|-----------------|--------|--------------|---------------------------|----------|
| Chen W, 2012      | China    | 74 040  | 33                        | 85.8% men Age at hire (y): 4.86±7.6 Current smokers: 48.0% Former smokers: 13.7% Duration of silica dust exposure (y): 18.7±10.4 | CVD: 4425 deaths Pulmonary heart disease: 2729 deaths Hypertensive heart disease: 391 deaths IHD: 624 deaths Chronic rheumatic heart disease: 123 deaths | 1.91 (1.85-1.98) 4.03 (3.87-4.2) 2.45 (2.17-2.75) 1.04 (0.94-1.14) 0.56 (0.45-0.69) | Metal mines and pottery factories | High     |
| Fan C, 2018       | Sweden   | 2551    | 25                        | Age at hire (y): 28±10.3 Years of employment: 11.7±11 Exposure for silica mg/m³: 0.48±0.58 | CVD Acute myocardial infarction | 1.41 (1.26-1.57) 0.73 (0.6-0.89) | Foundry                  | High     |
| Merlo F, 1995     | Italy    | 515     | 26                        | Age (y): 55.3±11.1 Mean length between first employment and the diagnosis of silicosis: 31.9±13.5 | CVD | 0.51 (0.36-0.71) | Diagnosed at the Department of Occupational Health of the San Martino Hospital | Low      |
| Miller BG, 2010   | England  | 45 000  | 47                        | Age (y): 15-64, Smokers: 75% Ex-smokers: 8% | CVD: 4890 deaths IHD: 3298 deaths | 0.98 (0.95-1.06) 1.00 (0.97-1.04) | Pneumoconiosis Field Research (PFR) Program | High     |
| Moulin J, 1992    | France   | 4227    | 16                        | Smokers: 24% | IHD | 1.12 (0.82-1.48) | Factory                  | Low      |
| Puntoni R, 1988   | Italy    | 231     | 19                        | - | CVD | 1.73 (1.04-2.69) | Factory | Low |
| Weiner J, 2007    | Sweden   | 11 896  | 25                        | Men 100% Age (y): 20-64 Smoking: 46% | IHD | 1.31 (1.24-1.38) | Miner, Factories Stone workers | High     |

SMR, Standard mortality ratio; CVD, Cardiovascular disease; IHD, Ischemic heart disease

### Authors

- **Chen et al.**
  - Year: 2012
  - Country: China
  - SMR (95% CI): 1.91 (1.85-1.98)
- **Fan et al.**
  - Year: 2018
  - Country: Sweden
  - SMR (95% CI): 1.41 (1.26-1.57)
- **Merlo et al.**
  - Year: 1995
  - Country: Italy
  - SMR (95% CI): 0.51 (0.36-0.71)
- **Miller et al.**
  - Year: 2010
  - Country: England
  - SMR (95% CI): 0.98 (0.95-1.06)
- **Moulin et al.**
  - Year: 1992
  - Country: France
  - SMR (95% CI): 1.12 (0.82-1.48)
- **Puntoni et al.**
  - Year: 1988
  - Country: Italy
  - SMR (95% CI): 1.73 (1.04-2.69)
- **Weiner et al.**
  - Year: 2007
  - Country: Sweden
  - SMR (95% CI): 1.31 (1.24-1.38)

Overall (I-squared=98.9%, p=0.001) SMR, Standard mortality ratio; CVD, Cardiovascular disease; IHD, Ischemic heart disease

Figure 2. Forest plot for the meta-analysis of the association between silica exposure and mortality due to cardiovascular disease.
oxygen species, and nitrogen species have been reported in silicosis progression. Chen et al., in a cohort study on 74,040 workers exposed to silica dust, observed a high mortality rate from all causes, especially CVD (ie, ischemic heart disease and hypertensive heart disease).

Silica exposure can lead to pulmonary fibrosis, which compromises lung function. Additionally, silica crystals have a close association with pulmonary inflammation. Inflammatory mediators pass through the blood circulation, including pulmonary and systemic circulations, and cause vascular injury. Very fine silica particles can also reach the vascular bed and disturb the integrity of the vascular endothelium. Recurrent injury to the pulmonary vasculature can result in the development of pulmonary hypertension. In animal models of silica exposure, high expressions of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of matrix metalloproteinase-1 (TIMP-1) in lung tissue, pulmonary vascular remodeling, medial thickening, and elevated right ventricular systolic pressure have been reported. These factors have mechanistic links with pulmonary vascular remodeling and pulmonary hypertension. Pulmonary hypertension may indicate a spectrum of wide cardiac dysfunction, and it is a determinant of heart failure. Pulmonary hypertension in patients with silicosis is associated with poor prognosis; consequently, it is crucial to diagnose it in its primary stage. Liu K et al indicated that silica exposure could increase heart disease, not least pulmonary heart disease. Liu Y et al, in a cohort study on 44,807 Chinese workers, reported an association between an increased risk of mortality from pulmonary heart disease and low levels of silica exposure. Murray et al, in a case-control study on 732 South African gold miners, confirmed the association between the presence and severity of silicosis and pulmonary heart disease. Likewise, Dong et al indicated the association between silicosis and mortality due to pulmonary heart disease. Also in this regard, Chen G et al detected right ventricular hypertrophy in patients suffering from silicosis, complicated by pulmonary heart disease.

As was noted, silica exposure causes adverse health effects, with the existing evidence even indicating that low levels of silica exposure may have unfavorable effects. Numerous workplaces have silica concentrations greater than the permissible exposure limit (PEL); however, the common PEL may fail to confer complete protection to workers. Furthermore, workers in low- and middle-income countries may become exposed to much higher concentrations of silica. Given the association between silica exposure and CVD, it seems vitally important that workers be educated about the use of personal protective equipment.

The present study comes with limitations and potential biases, some of which are inherent in systematic reviews generally. An important concern is the presence of biases and confounding items, which is innate in human studies. For instance, age, smoking, and co-exposures are of great significance in mortality studies. In addition, studies may have been specifically susceptible to the misclassification of silica exposure. Unfortunately, because of the mismatch in the silica exposure classification, we excluded some works in the literature. It is worthy of note that the years of silica exposure may play a significant role in CVD mortality. Such potential confounders should, therefore, be taken into consideration in future research on the associations between environmental exposure and CVD mortality.

**Conclusion**

The results of the current study confirm that silica exposure is associated with an enhanced risk of mortality due to hypertensive and pulmonary heart diseases. The verification of these results may have important effects on basic prevention strategies for health implications, especially for workers’ health.

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