



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-

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income countries.²

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.⁴ Volcanic explosions, windblown soils, and dust storms are the natural sources of crystalline silica.⁵ Generally, exposure to crystalline silica is one of the most critical occupational risks.⁶ Strong epidemiologic evidence confirms the association between occupational silica exposure and different diseases such as silicosis, lung cancer, pulmonary tuberculosis, chronic obstructive pulmonary disease,⁷ rheumatoid arthritis,⁸ and renal disease.⁹

In recent years, studies have focused more on the influence of environmental factors on the incidence of CVD.¹⁰ Exposure to environmental pollutants has a significant function in the development and severity of CVD.¹ 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).¹¹ 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 χ^2 test and I^2 statistics.¹² In this research, I^2 of less than 25 denotes low heterogeneity, I^2 of 25% to 50% moderate heterogeneity, and I^2 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.^{13–15} Stata software, version 13 (Stata Corp, College Station, TX, USA), was used for the statistical analyses, and a P-value of less than 0.05 was regarded as statistically significant.

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 irrelative 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

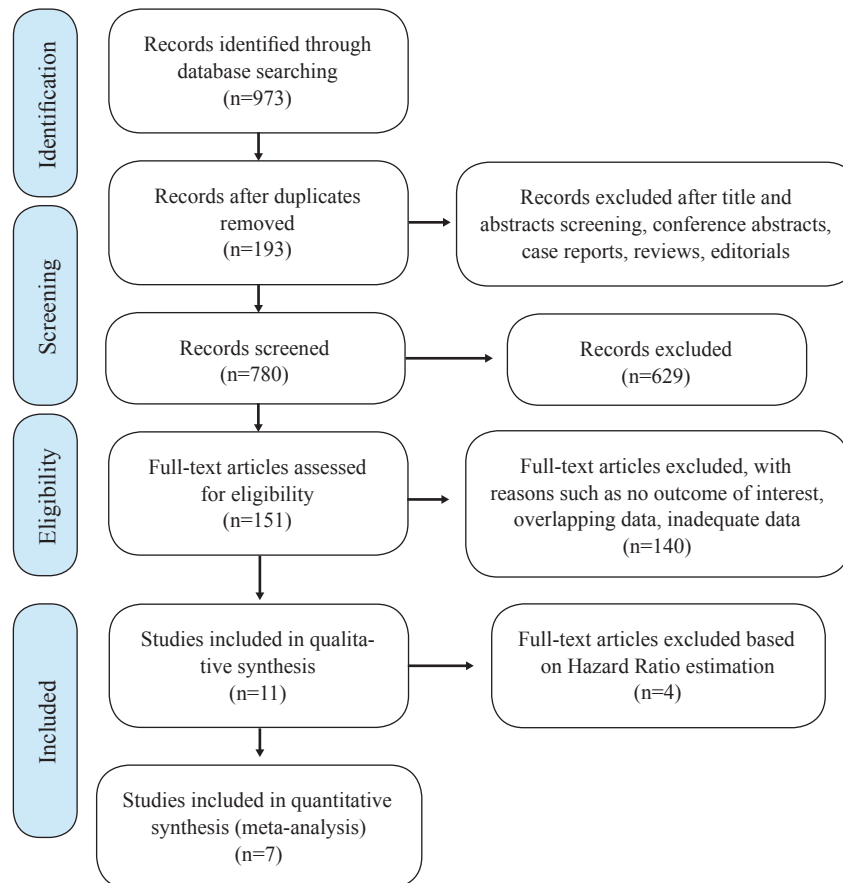


Figure 1. Flow diagram of the literature search

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.¹⁶⁻¹⁸ CVD mortality was evaluated in 4 studies,^{16, 18-21} ischemic heart disease in 4 studies,^{16, 17, 20, 22} and hypertensive and pulmonary heart diseases in 1 study.¹⁶ The sample sizes ranged from 213 to 74 040 workers. The duration of follow-up varied from 16 years to 47 years.^{20, 22}

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.²³ Inflammation is involved in the development of hypertension via arterial stiffness.²⁴ A growing body of evidence indicates that oxidative stress and inflammation are the major mechanisms for hypertension development.²⁵ Silica dust can produce reactive oxygen species and increase oxidative stress.²⁶ 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 ¹⁶	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 ¹⁸	Sweden	2551	25	Age at hire (y): 28±10.3 Years of employment: 11.7±11 Exposure for silica mg/m ³ : 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 ¹⁹	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 ²⁰	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 ²²	France	4227	16	Smokers: 24%	IHD	1.12 (0.82-1.48)	Factory	Low
Puntoni R, 1988 ²¹	Italy	231	19	-	CVD	1.73 (1.04-2.69)	Factory	Low
Weiner J, 2007 ¹⁷	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

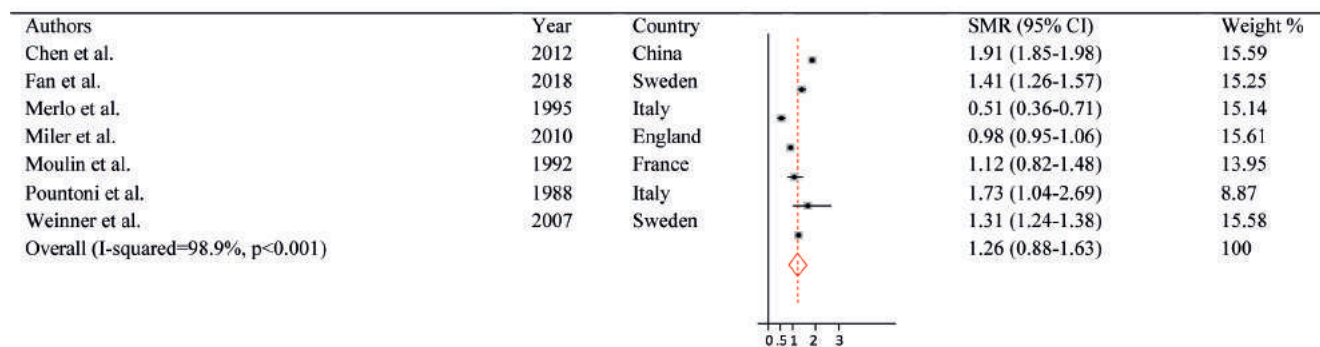


Figure 2. Forest plot for the meta-analysis of the association between silica exposure and mortality due to cardiovascular disease

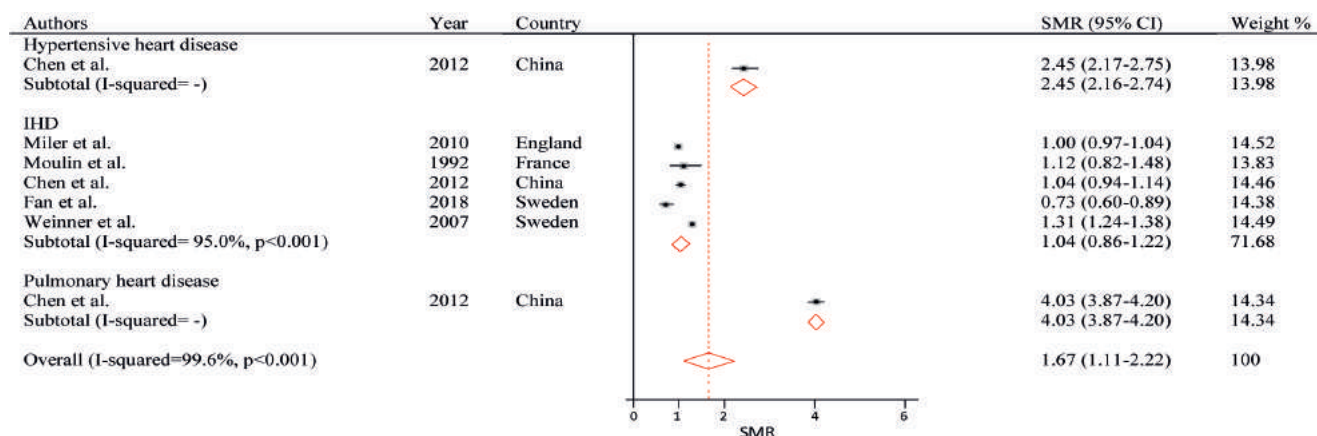


Figure 3. Forest plot for the meta-analysis of the association between silica exposure and mortality based on the type of cardiovascular disease

oxygen species, and nitrogen species have been reported in silicosis progression.²⁷ Chen et al,¹⁶ 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.²⁸ Additionally, silica crystals have a close association with pulmonary inflammation.²⁹ 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.³⁰ Recurrent injury to the pulmonary vasculature can result in the development of pulmonary hypertension.³¹ 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.³¹ Pulmonary hypertension may indicate a spectrum of wide cardiac dysfunction,³² and it is a determinant of heart failure.³³ Pulmonary hypertension in patients with silicosis is associated with poor prognosis; consequently, it is crucial to diagnose it in its primary stage.³⁴ Liu K et al³⁵ indicated that silica exposure could increase heart disease, not least pulmonary heart disease. Liu Y et al,³⁶ 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,³⁷ 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 al³⁸ indicated the association between silicosis and mortality due to pulmonary heart disease. Also in this regard, Chen G et al³⁹ 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.⁴⁰ Numerous workplaces have silica concentrations greater than the permissible exposure limit (PEL); however, the common PEL may fail to confer complete protection to workers.³⁶ Furthermore, workers in low- and middle-income countries may become exposed to much higher concentrations of silica.⁴¹ 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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References

1. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015;12:627-642.
2. World Health Organization. Global status report on noncommunicable diseases 2010. <https://b2n.ir/900199> (5 Dec 2019).
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carmahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224-2260.
4. Guo J, Shi T, Cui X, Rong Y, Zhou T, Zhang Z, Liu Y, Shen Y, Chen W. Effects of silica exposure on the cardiac and renal inflammatory and fibrotic response and the antagonistic role of interleukin-1 beta in C57BL/6 mice. *Arch Toxicol* 2016;90:247-258.
5. De Berardis B, Incocciati E, Massera S, Gargaro G, Paoletti L. Airborne silica levels in an urban area. *Sci Total Environ* 2007;382:251-258.
6. Liu Y, Rong Y, Steenland K, Christiani DC, Huang X, Wu T, Chen W. Long-term exposure to crystalline silica and risk of heart disease mortality. *Epidemiology* 2014;25:689-696.
7. The Global Occupational Health Network. Elimination of silicosis. <https://b2n.ir/438391> (5 Dec 2019)
8. Mehri F, Jenabi E, Bashirian S, Shahna FG, Khazaei S. The association between occupational exposure to silica and risk of developing rheumatoid arthritis: a meta-analysis. *Saf Health Work* 2020;11:136-142.
9. Steenland K, Sanderson W, Calvert GM. Kidney disease and arthritis in a cohort study of workers exposed to silica. *Epidemiology* 2001;12:405-412.
10. Fang SC, Cassidy A, Christiani DC. A systematic review of occupational exposure to particulate matter and cardiovascular disease. *Int J Environ Res Public Health* 2010;7:1773-1806.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;327:557-560.
13. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-1101.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.
15. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046-1055.
16. Chen W, Liu Y, Wang H, Hnizdo E, Sun Y, Su L, Zhang X, Weng S, Bochmann F, Hearl FJ, Chen J, Wu T. Long-term exposure to silica dust and risk of total and cause-specific mortality in Chinese workers: a cohort study. *PLoS Med* 2012;9:e1001206.
17. Weiner J, Barlow L, Sjögren B. Ischemic heart disease mortality among miners and other potentially silica-exposed workers. *Am J Ind Med* 2007;50:403-408.
18. Fan C, Graff P, Vihlborg P, Bryngelsson IL, Andersson L. Silica exposure increases the risk of stroke but not myocardial infarction—a retrospective cohort study. *PLoS One* 2018;13:e0192840.
19. Merlo F, Fontana L, Reggiardo G, Ceppi M, Barisione G, Garrone E, Doria M. Mortality among silicotics in Genoa, Italy, from 1961 to 1987. *Scand J Work Environ Health* 1995;21 Suppl:77-80.
20. Miller BG, MacCalman L. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. *Occup Environ Med* 2010;67:270-276.
21. Puntoni R, Goldsmith DF, Valerio F, Vercelli M, Bonassi S, Di Giorgio F, Ceppi M, Stagnaro E, Filiberti R, Santi L. A cohort study of workers employed in a refractory brick plant. *Tumori* 1988;74:27-33.
22. Moulin JJ, Wild P, Mantout B, Fournier-Betz M, Mur JM, Smaghe G. Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control* 1993;4:75-81.
23. Redon J, Tellez-Plaza M, Orozco-Beltran D, Gil-Guillen V, Pita Fernandez S, Navarro-Pérez J, Pallares V, Valls F, Fernandez A, Perez-Navarro AM, Sanchis C, Dominguez-Lucas A, Sanz G, Martin-Moreno JM; ESCARVAL Study Group. Impact of hypertension on mortality and cardiovascular disease burden in patients with cardiovascular risk factors from a general practice setting: the ESCARVAL-risk study. *J Hypertens* 2016;34:1075-1083.
24. De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. *Curr Hypertens Rep* 2015;17:507.
25. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. *Hypertens Res* 2011;34:431-440.
26. Orman A, Kahraman A, Cakar H, Ellidokuz H, Serteser M. Plasma malondialdehyde and erythrocyte glutathione levels in workers with cement dust-exposure [corrected]. *Toxicology* 2005;207:15-20.
27. Fubini B, Hubbard A. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. *Free Radic Biol Med* 2003;34:1507-1516.



28. Zelko IN, Zhu J, Roman J. Role of SOD3 in silica-related lung fibrosis and pulmonary vascular remodeling. *Respir Res* 2018;19:221.
29. Sellamuthu R, Umbright C, Roberts JR, Chapman R, Young SH, Richardson D, Cumpston J, McKinney W, Chen BT, Frazer D, Li S, Kashon M, Joseph P. Transcriptomics analysis of lungs and peripheral blood of crystalline silica-exposed rats. *Inhal Toxicol* 2012;24:570-579.
30. Nemmar A, Vanbilloen H, Hoylaerts MF, Hoet PH, Verbruggen A, Nemery B. Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. *Am J Respir Crit Care Med* 2001;164:1665-1668.
31. Zelko IN, Zhu J, Ritzenthaler JD, Roman J. Pulmonary hypertension and vascular remodeling in mice exposed to crystalline silica. *Respir Res* 2016;17:160.
32. Tang M, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. *Am J Kidney Dis* 2018;72:75-83.
33. Shin JT, Semigran MJ. Heart failure and pulmonary hypertension. *Heart Fail Clin* 2010;6:215-222.
34. Evers H, Liehs F, Harzbecker K, Wenzel D, Wilke A, Piesch W, Schauer J, Nahrendorf W, Preisler J, Luther R. Screening of pulmonary hypertension in chronic obstructive pulmonary disease and silicosis by discriminant functions. *Eur Respir J* 1992;5:444-451.
35. Liu K, Mu M, Fang K, Qian Y, Xue S, Hu W, Ye M. Occupational exposure to silica and risk of heart disease: a systematic review with meta-analysis. *BMJ Open* 2020;10:e029653.
36. Liu Y, Zhou Y, Hnizdo E, Shi T, Steenland K, He X, Chen W. Total and cause-specific mortality risk associated with low-level exposure to crystalline silica: a 44-year cohort study from China. *Am J Epidemiol* 2017;186:481-490.
37. Murray J, Reid G, Kielkowski D, de Beer M. Cor pulmonale and silicosis: a necropsy based case-control study. *Br J Ind Med* 1993;50:544-548.
38. Dong D, Xu G, Sun Y, Hu P. Lung cancer among workers exposed to silica dust in Chinese refractory plants. *Scand J Work Environ Health* 1995;21 Suppl 2:69-72.
39. Chen G. Study on tissue Doppler imaging in diagnosis of right ventricular hypertrophy in patients with silicosis complicated by chronic pulmonary heart disease. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2014;32:931-933.
40. Swanepoel AJ, Rees D, Renton K, Swanepoel C, Kromhout H, Gardiner K. Quartz exposure in agriculture: literature review and South African survey. *Ann Occup Hyg* 2010;54:281-292.
41. Steenland K, Ward E. Silica: a lung carcinogen. *CA Cancer J Clin* 2014;64:63-69.