BMJ Open

Occupational exposure to silica and risk of heart disease: a systematic review with meta-analysis

Kai Liu 1, Min Mu 2, Kehong Fang 3, Yuanyuan Qian 1, Song Xue 4, Weijiang Hu 5, Meng Ye 1

ABSTRACT

Objective To search for evidence of the relationship between occupational silica exposure and heart disease.

Design A systematic review and meta-analysis.

Background Growing evidence suggests a relationship between occupational silica exposure and heart disease; however, the link between them is less clear.

Data sources PubMed, ScienceDirect, Springer and EMBASE were searched for articles published between 1 January 1995 and 20 June 2019. Articles that investigated the effects of occupational silica exposure on the risk of heart disease were considered.

Study selection We included cohort studies, including prospective, retrospective and retrospective studies.

Data extraction and synthesis We extracted data using a pilot data collection form and conducted random-effects meta-analysis and exposure-response analysis. The meta-relative risk (meta-RR), a measure of the average ratio of heart disease rates in those with and without silica exposure, was used as an inverse variance-weighted average of relative risks from the individual studies. The Newcastle-Ottawa Quality Assessment Scale for cohort studies was used for study quality assessment.

Outcome measure We calculated the risk of heart diseases such as pulmonary heart disease, ischaemic heart disease and others.

Results Twenty cohort studies were included. The results suggest a significant increase in the risk of overall heart disease (meta-RR=1.08, 95% CI 1.03 to 1.13). Stronger evidence of association with pulmonary heart disease was found in the risk estimate of both categories of heart disease (meta-RR=1.24, 95% CI 1.08 to 1.43) and in the exposure-response analysis (meta-RR=1.39, 95% CI 1.19 to 1.62). Our subgroup analyses also revealed that the statistical heterogeneity among studies could be attributed mainly to the diversity in reference group, occupation and study quality score.

Conclusions Silica-exposed workers are at an increased risk for overall heart disease, especially pulmonary heart disease. Further research is needed to better clarify the relationship between occupational silica exposure and ischaemic heart disease.

PROSPERO registration number CRD42019124673.

INTRODUCTION

Silica is the key ingredient of dust, with widespread human exposure in a working environment. Occupational silica exposure has long been recognised as a threat to workers' health, causing diseases that include autoimmune diseases, silicosis, tuberculosis, lung cancer and other non-malignant respiratory diseases.1-10 Although the International Agency for Research on Cancer has classified respirable crystalline silica as a human carcinogen in 1997, there are still a large number of workers exposed to silica.11-12 The US Occupational Safety and Health Administration estimated that there were about 2.2 million American workers exposed to silica in 2016.12

There has been increasing recognition that occupational silica exposure may be responsible for heart diseases, with several epidemiological studies showing that cardiovascular disease (CVD) mortality is significantly higher in silica-exposed workers, although at different concentrations.13-21 Nevertheless, the link between silica exposure and risk of heart disease mortality or morbidity is still controversial, especially ischaemic heart disease. Fan et al.13 revealed that Swedish foundry workers exposed to respirable silica did not exhibit elevated morbidity and mortality from myocardial infarction. However, some earlier research came to opposite conclusions.14-22-27

Strengths and limitations of this study

- We used comprehensive and robust search strategy, including a broad literature search and a piloted data collection.
- Sensitivity analysis was conducted to examine the influence of specific studies on overall heart disease.
- Subgroup analyses and exposure-response analyses were also performed.
- A major limitation was the high heterogeneity among studies, precluding to some degree firm conclusions.
- There were few articles included in the exposure-response analyses.
In 1997, Sjogren published a review article on ischaemic heart disease among quartz-exposed workers. The author concludes that stonemasons, carvers and African gold miners are at a high risk for myocardial infarction or ischaemic heart disease, but this could not be explained by differences in smoking habits or different sample sizes. On this background, we conducted a systematic literature review and meta-analysis of occupational silica exposure and heart disease.

**METHODS**

We performed a systematic review and meta-analysis according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The objective was formulated using the PICOS criteria (PICO: population: workers; intervention: exposure to respirable silica and other particle sizes) and exposure type (including silica dust with asbestos, silica mixed dust and silica dust exposure type (including silica dust with asbestos, silica mixed dust and silica dust without asbestos, silica mixed dust and silica dust without asbestos) and exposure assessment method (including sample monitoring, job exposure matrix or approximation), exposure type (including silica dust with asbestos, silica dust without asbestos, silica mixed dust and silica dust with trichloroethylene), silica particle size (including respirable silica and other particle sizes) and exposure level (mg/m³-years).

**Outcome definition**

The main outcome was heart disease fulfilling the International Classification of Diseases 6, 7, 8, 9 and 10 criteria. Categories of heart disease mainly included pulmonary heart disease, ischaemic heart disease and other heart diseases. Ischaemic heart disease included myocardial infarction and coronary heart disease. Other heart diseases included hypertensive heart disease and chronic rheumatic heart disease. Furthermore, there were six articles that reported only the risk of ‘all heart disease’, so we classified ‘all heart disease’ as the fourth category, including CVD. Standardised mortality ratio for underlying ischaemic heart disease was included in our analyses.

**Study quality assessment**

The Newcastle-Ottawa Quality Assessment Scale for cohort studies was used for quality assessment and one point for every satisfactory answer. Eight items were assessed to calculate study quality score: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of design or analysis, assessment of outcome, follow-up long enough for outcomes to occur or not, and adequacy of follow-up (online supplementary file 2).

**Study and data collection processes**

Four authors (KL, MY, MM and WH) designed this study. MY and WH assessed the full-text articles according to the exclusion and inclusion criteria. Two reviewers (KL and MM) extracted the study characteristics, outcomes and study quality data using a piloted data collection form. Only studies with high methodological quality, that is, with a score of 6 or higher, were included. All reviewers independently reviewed the titles and abstracts of all identified citations. Disagreements were resolved by discussion and consensus, with MM as an adjudicator.

**Statistical analysis**

The relative risk or coefficient value is ordinarily not constant across study populations. Pooled statistics could be a useful summary but generally cannot be an accurate estimate. The SE and confidence limits for the common effect could not adequately reflect the variability and range of accurate effect if important heterogeneity is present. Thus, we used random-effects model to calculate the meta-relative risk (meta-RR), a measure of the average ratio of heart disease rates in those with and without silica exposure, as an inverse variance-weighted average of relative risks from the individual studies. We calculated the variance estimate, $\hat{\Phi}$, as a measure of heterogeneity among studies. The weight of the result was computed from the individual original estimate SE as 1/SE. All statistical analyses were performed using STATA V.15.0 (metan, metabias and funnel commands).

First, we assessed publication bias by conducting Egger’s linear regression test. Second, sensitivity analysis was performed to account for bias in study selection. Third, we conducted subgroup analyses stratified by study reference group, occupation, duration of follow-up, adjustment for smoking, year of publication, sample size,
Liu K, et al. BMJ Open 2020;10:e029653. doi:10.1136/bmjopen-2019-029653

Figure 1 Flow chart of study selection for meta-analysis.

study quality score, race, gender, exposure measurement method, exposure assessment method, exposure type, research category and silica particle size. Fourth, we conducted exposure-response analyses for ischaemic and pulmonary heart disease using penalised spline models. The original cumulative silica exposure data (mg/m$^3$-years) were estimated by linking a job exposure matrix to each person’s work history. Moreover, an overall p value of testparm doses results was calculated to test the linearity in exposure-response analyses: p for linearity trend $>$0.05; p for non-linearity trend $<$0.05. Midpoints of cumulative silica exposure categories were used for dose-response calculations. If cumulative silica exposure intervals were provided, the midpoint between the lower and upper bounds was regarded as the corresponding cumulative silica exposure dose. For open-ended upper and lower categories, midpoints were calculated separately as the lower boundary multiplied by 1.2 or as the upper boundary divided by 1.2.34

Patient involvement
Patients or the public were not directly involved in the study. We used data from published papers only.

RESULTS
Overview of studies included in the systematic review
Study selection is described in figure 1. We identified 2838 articles: 2608 of the original literature search (from 1 January 1995 to 22 December 2018) and 230 new articles from the updated search but none included in the analysis (from 23 December 2018 to 20 June 2019). Case reports, reviews, letters and papers not related to heart disease were excluded. This left 223 articles for full-text review. A total of 203 articles were excluded after full-text review for the following reasons: (1) 101 were not on occupational exposure to silica; (2) 49 were duplicate publications on the same population; (3) 23 did not provide specific occupational exposure data such as whether low-level dust was equal to occupational silica exposure $>$0 mg/m$^3$;35 (4) 27 were based on patients with pneumoconiosis; and (5) 3 were of poor quality. The remaining 20 articles reported 28 original heart disease risk estimates and were included in the meta-analysis.

Table 1 and online supplementary file 2 show the characteristics of the included studies. The sample size of studies ranged from 1817 to 74 040. Seven studies were conducted in China, six in the USA, three in Sweden, three in the UK and one in South Africa. Two studies reported the risk of ischaemic heart disease incidence,13 15 and 19 reported on the risk of heart disease mortality.7–10 13 14 16–27 Categories of heart diseases ranged from ischaemic heart disease and pulmonary heart disease, to other heart diseases. A total of 14 studies provided data on the risk of ischaemic heart disease, including myocardial infarction and coronary heart disease6–10 13–23; 5 reported on the risk of pulmonary heart disease7 9 10 14 17; and 2 discussed the risk of other heart diseases.10 14 All 20 studies had quality scores ranging from 6 to 9, with 9 studies having high quality score of $\geq$8.6 10 14–18 22 24

Overall and categories of heart disease risk estimate
The relationship between occupational silica exposure and overall heart disease is shown in figure 2. The results suggest a significant increase in overall heart disease risk (meta-RR=1.08, 95% CI 1.03 to 1.13, $I^2$=96.0%, p<0.05).

In the risk estimate analysis of heart disease categories (figure 2), ischaemic heart disease presented a slight but non-significant increase (meta-RR=1.07, 95% CI 1.00 to 1.16, p=0.058), while statistically significant positive association was observed for pulmonary heart disease (meta-RR=1.24, 95% CI 1.08 to 1.43, p=0.002). Analysis of studies with other heart diseases showed a slight decrease (meta-RR=0.96, 95% CI 0.94 to 0.99, p=0.002).

Publication bias
Egger’s linear regression test indicated that there was no publication bias (p=0.446, 95% CI −1.308 to 2.890) (figure 3).

Sensitivity analysis
We deleted one risk estimate from the overall meta-risk estimate each time to check the effect of the removed data. Sensitivity analysis indicated that 12 studies and pulmonary heart disease mortality data from Dong et al and Lai et al were the main origin of heterogeneity.5 8–10 13 14 16 20 21 23–27 The heterogeneity decreased significantly after excluding the risk estimates of the main origin of heterogeneity (before exclusion: $I^2$=96.0%, p=0.000; after exclusion: $I^2$=35.3%, p=0.135), while the positive association between occupational silica exposure and heart disease was not materially changed (meta-RR=1.14, 95% CI 1.08 to 1.20, p=0.000).
Table 1  Summary information of cohort studies on silica-exposed workers, published between 1 January 1995 and 20 June 2019

| Authors and year of publication | Country and study population | Employment period | Follow-up period, outcome | Heart disease (ICD codes) | Deaths/cases | SMR/(S)RR/HR (95% CI)* |
|---------------------------------|-----------------------------|-------------------|---------------------------|---------------------------|--------------|--------------------------|
| **Lu et al (2012)**15           | China, 1817 workers (1318 male and 499 female) in automobile foundry. | 1980–1996         | 1980–2009 Incidence       | Ischaemic heart disease (ICD: unspecified) | 156          | 1.46 (1.02 to 2.08)     |
| **Fan et al (2018)**13          | Sweden, 2551 male workers in 11 foundries. | 1913–2005         | 1987–2012 Mortality Incidence | Cardiovascular disease (ICD-10 codes) Myocardial infarction (ICD-10: I21–I22) | 338          | 1.41 (1.26 to 1.57) 0.73 (0.60 to 0.89) Incidence 1.00 (0.90 to 1.10) |
| **Vacek et al (2011)**8         | USA, 7052 male workers in granite industry. | 1947–1998         | 1947–2004 Mortality       | All heart diseases (ICD-9 codes) | 1219         | 0.89 (0.84 to 0.94)  |
| **Dong et al (1995)**9          | China, 17 696 male workers at 11 refractory plants and 10 rolling steel mills. | Before 1962–1985  | 1962–1995 Mortality       | Pulmonary heart disease (ICD-7 codes) Coronary heart disease (ICD-7 codes) | 338          | 1.41 (1.26 to 1.57) 0.73 (0.60 to 0.89) Incidence 1.00 (0.90 to 1.10) |
| **Weiner et al (2007)**16       | Sweden, 11 896 male mine and stone workers. | 1970–1995         | 1970–1995 Mortality       | Pulmonary heart disease (ICD-8 and ICD-9 codes) | 1432         | 1.31 (1.24 to 1.38)  |
| **Liu et al (2014)**14          | China, 42 572 workers (36 168 male and 6404 female) at 29 metal mines and pottery factories. | 1915–1974         | 1960–2003 Mortality       | Pulmonary heart disease (ICD-10: I20–I25) Hypertensive heart disease (ICD-10: I05–I09) | 1528         | 1.30 (1.26 to 1.33) 0.98 (0.94 to 1.02) 0.96 (0.92 to 1.00) 0.93 (0.89 to 0.96) |
| **Lai et al (2018)**8           | China, 7665 workers (6542 male and 1123 female) in 1 iron mine company. | 1960–1974         | 1960–2012 Mortality       | Pulmonary heart disease (ICD-8- ICD-9 codes) | 219          | 1.13 (0.99 to 1.30) 1.35 (1.20 to 1.53) |
| **Chen et al (2012)**10         | China, 74 040 workers (63 529 male and 10511 female) at 20 metal mines and 9 pottery factories. | 1915–1974         | 1960–2003 Mortality       | Pulmonary heart disease (ICD-10: I20–I25) Hypertensive heart disease (ICD-10: I05–I09) | 2729         | 1.05 (1.04 to 1.06) 0.98 (0.96 to 1.00) 0.97 (0.95 to 0.99) 0.98 (0.93 to 1.03) |
| **Liu et al (2017)**17          | China, 44 807 workers (36 400 male and 8407 female) at 10 tungsten mines. | 1915–1974         | 1960–2003 Mortality       | Ischaemic heart disease (ICD-10: I20-I25) Pulmonary heart disease (ICD-10: I26–I27) | 384          | 2.99 (1.67 to 5.33) 5.48 (3.47 to 8.65) |
| **Radican et al (2008)**22      | USA, 14 455 workers (10 730 male and 3725 female) at Hill Air Force Base. | Before 1952–1956  | 1952–2000 Mortality       | Ischaemic heart disease (ICD-10: I20-I25) | 143          | 1.50 (1.00 to 2.24)  |
| **Steenland et al (2001)**17    | USA, 4851 workers (4569 male and 51 female) in 18 industrial sand plants. | 1960–1978         | 1974–1996 Mortality       | Ischaemic heart disease (ICD-8: 410–414) | 330          | 1.22 (1.09 to 1.36)  |
| **Bjor et al (2010)**18         | Sweden, 13 621 male workers at 2 iron-ore mines. | 1923–1996         | 1952–2001 Mortality       | Ischaemic heart disease (ICD-7 to ICD-10) | 1166         | 1.15 (1.02 to 1.31)  |
| **Graham et al (2004)**23       | USA, 5408 male workers at granite sheds and quarries. | Before 1940–1982  | 1950–1996 Mortality       | Ischaemic heart disease (ICD-8 codes) | 710          | 0.74 (0.69 to 0.80)  |
| **Miller et al (2010)**24       | UK, 17 820 male workers at 10 British collieries. | Before 1950–1992  | 1959–2006 Mortality       | Ischaemic heart disease (ICD-7 to ICD-10) | 3346         | 0.99 (0.96 to 1.02)  |

Continued
Table 1 Continued

| Authors and year of publication | Country and study population | Employment period | Follow-up period, outcome | Heart disease (ICD codes) | Deaths/cases | SMR/(S)RR/HR (95% CI)* |
|--------------------------------|------------------------------|-------------------|--------------------------|---------------------------|--------------|-----------------------|
| Checkoway et al (1997)          | USA, 2342 male workers at a diatomaceous earth industry. | Before 1942–1987 | 1942–1994 Mortality | Ischaemic heart disease (ICD-5 to ICD-9) | 191 | 0.82 (0.71 to 0.95) |
| Cherry et al (2013)             | UK, 5115 male workers at pottery industry. | Before 1960–2008 | 1985–2008 Mortality | All heart diseases (ICD-9: 391–429) (ICD-10: 101–151) | 609 | 1.00 (0.92 to 1.08) |
| McDonald et al (2005)           | USA, 2670 male workers at sand industry. | Before 1980–1994 | 1980–2000 Mortality | All heart diseases (ICD-9: 380.0–389.9, 402.0–402.9, 404.0, 410.0–519.9) | 369 | 1.11 (0.97 to 1.27) |
| Cherry et al (1998)             | UK, 5115 male workers at pottery industry. | Before 1960–1992 | 1985–1992 Mortality | All heart diseases (ICD-9: 391–429) | 171 | 1.36 (1.16 to 1.58) |
| Reid et al (1996)               | South Africa, 4925 male workers at a gold mine. | Before 1970–1989 | 1970–1989 Mortality | Ischaemic heart disease (ICD-9: 410–414) | 687 | 1.24 (1.15 to 1.34) |
| Zhang et al (2008)              | China, 4851 workers (3560 male and 1291 female) at 3 ceramic factories. | 1972–1974 | 1972–2003 Mortality | Cardiovascular disease (ICD: unspecified) | 294 | 0.77 (0.61 to 0.98) |

*If a paper provides both SMR and RR values, the RR value is presented.

ICD, International Classification of Diseases; RR, relative risk; SMR, standardised mortality ratio; SRR, standardised rate ratio.

Subgroup analyses

We conducted subgroup analyses by study reference group, occupation, duration of follow-up, adjustment for smoking, race, year of publication, sample size, study quality score, gender, exposure measurement method, exposure assessment method, exposure type, research category and silica particle size (table 2). The results of subgroup analyses revealed significantly increased risk of heart disease, especially in the analysis of studies with external control (meta-RR=1.53, 95% CI 1.19 to 1.95, $I^2=43.2\%$, $p=0.152$), with a study quality score of 6 (meta-RR=1.35, 95% CI 1.17 to 1.57, $I^2=69.8\%$, $p=0.019$) and with qualitative exposure measurement method (meta-RR=1.37, 95% CI 1.06 to 1.76, $I^2=67.6\%$, $p=0.046$). Meanwhile, positive associations were limited, such as in the analysis of studies with 50–58 years of follow-up, with a quality score of 7 and with mean exposure measurement. The statistical heterogeneity among studies could...
### Table 2  Subgroup analyses of silica exposure and heart disease

| Study characteristics | Category                                      | Cohorts (n) | $\chi^2$ value (%) | P value for heterogeneity | Meta-RR (95% CI) | Tau²  |
|-----------------------|-----------------------------------------------|-------------|---------------------|---------------------------|------------------|-------|
| **Reference group**   |                                               |             |                     |                           |                  |       |
|                       | Internal control                              | 7           | 96.8                | 0.000                     | 1.04 (0.99 to 1.09) | 0.0079 |
|                       | External control                              | 3           | 43.2                | 0.152                     | 1.53 (1.19 to 1.95) | 0.0272 |
|                       | Total population control                       | 10          | 96.2                | 0.000                     | 1.09 (0.95 to 1.25) | 0.0466 |
| **Occupation**        |                                               |             |                     |                           |                  |       |
|                       | Iron and steel foundry workers                 | 3           | 75.7                | 0.006                     | 1.38 (1.03 to 1.84) | 0.0614 |
|                       | Mine and stone foundry workers                 | 15          | 96.6                | 0.000                     | 1.04 (1.00 to 1.09) | 0.0104 |
|                       | Other unspecified workers                      | 2           | 0.0                 | 0.745                     | 1.42 (1.27 to 1.58) | 0.0000 |
| **Duration of follow-up** |                                           |             |                     |                           |                  |       |
|                       | 8–25                                          | 6           | 80.6                | 0.000                     | 1.21 (1.08 to 1.36) | 0.0163 |
|                       | 26–32                                         | 4           | 87.2                | 0.000                     | 1.24 (1.03 to 1.50) | 0.0306 |
|                       | 33–49                                         | 7           | 97.2                | 0.000                     | 1.03 (0.98 to 1.09) | 0.0086 |
|                       | 50–58                                         | 3           | 93.7                | 0.000                     | 0.96 (0.77 to 1.22) | 0.0447 |
| **Adjustment for smoking** |                                      |             |                     |                           |                  |       |
|                       | Yes                                           | 8           | 96.6                | 0.000                     | 1.06 (1.01 to 1.11) | 0.0080 |
|                       | No                                            | 12          | 95.2                | 0.000                     | 1.11 (0.97 to 1.26) | 0.0522 |
| **Race**              |                                               |             |                     |                           |                  |       |
|                       | Yellow                                        | 7           | 96.6                | 0.000                     | 1.06 (1.01 to 1.12) | 0.0090 |
|                       | White                                         | 13          | 95.4                | 0.000                     | 1.01 (0.99 to 1.22) | 0.0306 |
| **Year of publication** |                                        |             |                     |                           |                  |       |
|                       | 1995–2001                                      | 6           | 88.1                | 0.000                     | 1.13 (0.95 to 1.34) | 0.0430 |
|                       | 2002–2008                                      | 4           | 97.7                | 0.000                     | 1.12 (0.82 to 1.54) | 0.0959 |
|                       | 2009–2015                                      | 7           | 97.3                | 0.000                     | 1.02 (0.97 to 1.07) | 0.0082 |
|                       | 2016–2018                                      | 3           | 84.2                | 0.000                     | 1.20 (1.08 to 1.33) | 0.0121 |
| **Sample size**       |                                               |             |                     |                           |                  |       |
|                       | <10000 participants                            | 11          | 94.3                | 0.000                     | 1.07 (0.94 to 1.22) | 0.0454 |
|                       | 10000–20 000 participants                      | 5           | 94.8                | 0.000                     | 1.24 (1.03 to 1.48) | 0.0360 |
|                       | >40000 participants                            | 4           | 97.5                | 0.000                     | 1.04 (0.98 to 1.10) | 0.0084 |
| **Study quality score** |                                       |             |                     |                           |                  |       |
|                       | 6                                              | 3           | 69.8                | 0.019                     | 1.35 (1.17 to 1.57) | 0.0132 |
|                       | 7                                              | 8           | 91.1                | 0.000                     | 1.00 (0.89 to 1.13) | 0.0292 |
|                       | 8                                              | 5           | 95.1                | 0.000                     | 1.22 (1.05 to 1.43) | 0.0310 |
|                       | 9                                              | 4           | 97.7                | 0.000                     | 1.03 (0.97 to 1.09) | 0.0083 |
| **Gender**            |                                               |             |                     |                           |                  |       |
|                       | Only male                                      | 12          | 95.4                | 0.000                     | 1.10 (0.99 to 1.22) | 0.0323 |
|                       | Male and female                               | 8           | 96.6                | 0.000                     | 1.07 (1.01 to 1.12) | 0.0089 |
| **Exposure measurement method** |                              |             |                     |                           |                  |       |
|                       | Qualitative exposure measurement               | 2           | 67.6                | 0.046                     | 1.37 (1.06 to 1.76) | 0.0332 |
|                       | Cumulative exposure measurement                | 17          | 95.7                | 0.000                     | 1.07 (1.03 to 1.12) | 0.0092 |
|                       | Mean exposure measurement                      | 1           | †                   | †                          | 0.79 (0.74 to 0.85) | 0.0000 |
| **Exposure assessment method** |                                    |             |                     |                           |                  |       |
|                       | Sample monitoring                             | 8           | 93.1                | 0.000                     | 1.07 (0.95 to 1.20) | 0.0265 |
|                       | Job exposure matrix                            | 7           | 96.9                | 0.000                     | 1.05 (1.00 to 1.11) | 0.0089 |
|                       | Approximation                                 | 5           | 83.3                | 0.000                     | 1.27 (1.06 to 1.52) | 0.0281 |

Continued
Exposure type

| Category                          | Coords (n) | I² value (%) | P value for heterogeneity | Meta-RR (95% CI) | Tau²  |
|----------------------------------|------------|--------------|---------------------------|-----------------|-------|
| Silica dust with asbestos        | 7          | 96.7         | 0.000                     | 1.06 (1.01 to 1.12) | 0.0092 |
| Silica mixed dust                | 8          | 96.4         | 0.000                     | 1.12 (0.96 to 1.30) | 0.0417 |
| Silica dust without asbestos     | 4          | 90.6         | 0.000                     | 1.06 (0.91 to 1.24) | 0.0219 |
| Silica dust with TCE             | 1†         | †            | †                         | 1.50 (1.00 to 2.25)§ | 0.0000 |

Research category

| Category                          | Coords (n) | I² value (%) | P value for heterogeneity | Meta-RR (95% CI) | Tau²  |
|----------------------------------|------------|--------------|---------------------------|-----------------|-------|
| Retrospective cohort study       | 4          | 87.8         | 0.000                     | 1.04 (0.80 to 1.36) | 0.0753 |
| Prospective cohort study         | 15         | 96.8         | 0.000                     | 1.07 (1.02 to 1.12) | 0.0106 |
| Retroprospective cohort study    | 1†         | †            | †                         | 1.24 (1.05 to 1.48) † |       |

Silica particle size

| Category                          | Coords (n) | I² value (%) | P value for heterogeneity | Meta-RR (95% CI) | Tau²  |
|----------------------------------|------------|--------------|---------------------------|-----------------|-------|
| Respirable silica                | 16         | 96.6         | 0.000                     | 1.07 (1.02 to 1.12) | 0.0107 |
| Other particle sizes             | 4          | 85.3         | 0.000                     | 1.28 (0.87 to 1.90) | 0.1667 |

*The exact 95% CI range is 0.998 to 1.092.
†Excluded due to lack of data or only one article giving an estimate.
‡The exact 95% CI range is 1.000 to 1.108.
§The exact 95% CI range is 1.002 to 2.245.
RR, relative risk; TCE, trichloroethylene.

be attributed mainly to the diversity in reference group, occupation and study quality score.

Exposure-response analyses

Our exposure-response analyses were based on four articles that reported the mortality risk (HR) of heart disease, with adjustment for gender, age at hire or year of birth, and smoking.

Statistically significant evidence of linear association was found between occupational silica exposure and pulmonary heart disease (p of testparm doses results=0.9627; figure 4). The meta-risk estimate of pulmonary heart disease was 1.39 (95% CI 1.19 to 1.62), while evidence of exposure-response analyses suggested a non-linear association between silica exposure and ischaemic heart disease (p of testparm doses results=0.000; figure 5). The meta-risk estimate of ischaemic heart disease dropped to 0.98, with no significance (95% CI 0.91 to 1.05), compared with the overall heart disease risk estimate (meta-RR=1.08).

Discussion

In this systematic review and meta-analysis, the association between occupational silica exposure and heart disease was investigated. Our results suggest that occupational silica exposure is associated with an increased risk of heart disease. Moreover, stronger evidence of positive associations with pulmonary heart disease was found in the risk estimate of both categories of heart disease and in the exposure-response analyses. In a meta-analysis of ischaemic heart disease studies, the risk of ischaemic heart disease was slightly increased, although not statistically significant. The positive association is consistent with previous studies. Our subgroup analyses also revealed that statistical heterogeneity was affected mainly by reference group, occupation and study quality score.

The diversity in the reference groups of the primary study might be a source of bias. Meta-analysis of studies with external control showed significantly increased risk for heart disease, but not for studies with total population control. This result might possibly be explained by
study showed that the impact of quartz dust on first acute myocardial infarction was observed only in a small subgroup that had virtually no pre-exposure to respirable quartz. This evidence might indicate a possible dynamic link among occupational silica exposure, respiratory disease, and ischaemic heart disease and stroke.

The biological mechanisms by which occupational silica exposure could increase the risk of heart disease are not well understood. Coal dust may cause upregulation of leucocyte recruiting factors and damage of alpha-1-antitrypsin (A1AT), while relative elevations in leucocyte count and A1AT deficiency are associated with increased cardiovascular risk. Moreover, silica might induce inflammation, which plays a key role in coronary artery disease.

**Strengths and limitations**

A major strength of the present study was the comprehensive and robust search strategy without any language restriction from all human cohort studies. A further strength was that we performed sensitivity analysis, subgroup analyses and exposure-response analyses. A major limitation was the high heterogeneity among studies, precluding to some degree firm conclusions. There were also few studies included in the exposure-response analyses.

**CONCLUSION**

This review demonstrates that occupational silica exposure is associated with increased risk of heart disease, especially pulmonary heart disease. Confirmation of this positive association may have an important implication on primary prevention strategies for silica-related heart diseases.

**Author affiliations**

1Department of Biomarkers and Molecular Epidemiology, National Institute of Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing, China
2Department of Public Health, School of Medicine, Anhui University of Science and Technology, Huaian, Anhui, China
3Department of Nutritional Epidemiology, National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention, Beijing, China
4Department of Orthopaedics, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
5Department of Occupational Epidemiology, National Institute of Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing, China

**Acknowledgements** We are sincerely grateful to the staff of the Chinese Center for Disease Control and Prevention, School of Medicine of the Anhui University of Science and Technology, and Orthopaedics of the Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine. We also would like to add a word of thanks to Shu-zhen Han for her grammatical corrections and suggestions.

**Contributors** KL, MY, MM and WH conceived and designed this study. KL, MM, KF, YYO and SX searched the data. MY and WH performed the study inclusion and assessment of risk of bias. The manuscript was written by KL. All authors contributed to reviewing the study outcomes and approved the final version of the manuscript.

**Funding** This study was supported by grants from the National Natural Science Foundation of China (81472956, 30972449) and by the Occupational Health Foundation of China (81472956, 30972449) and by the Occupational Health Foundation of China.
REFERENCES

1 Rocha-Parise M, Santos LMB, Damoisauxes JGMC, et al. Lymphocyte activation in silica-exposed workers. Int J Hyg Environ Health 2014;217:586–91.

2 Anlar HG, Bacanli M, Iritas S, et al. Effects of occupational silica exposure on oxidative stress and immune system parameters in ceramic workers in turkey. J Toxicol Environ Health A 2017;80:688–96.

3 Siribaddana AD, Wickramasekera K, Palipana WM, et al. A study on silicosis among employees of a silica processing factory in the central province of Sri Lanka. Ceylon Med J 2016;61,6:10.

4 Farazi A, Jabbarzadeh M. Silico-tuberculosis and associated risk factors in central province of Iran. Pan Afr Med J 2015;20:33:3.

5 Keil AP, Richardson DB, Westreich D, et al. Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality. Epidemiology 2018;29:65:65–65.

6 Lai H, Liu Y, Zhou M, et al. Combined effect of silica dust exposure and cigarette smoking on total and cause-specific mortality in iron miners: a cohort study. Environ Health 2018;17:46.

7 Steenland K, Sanderson W. Lung cancer among industrial sandworkers exposed to crystalline silica. Am J Epidemiol 2001;153:695–703.

8 Vacek PM, Verma DK, Graham WG, et al. Mortality in Vermont granite workers and its association with silica exposure. Occup Environ Med 2011;68:312–8.

9 Dong D, Xu G, Sun Y, et al. Mortality from myocardial infarction in relation to exposure to vibration and dust among a cohort of iron-ore miners in Sweden. Occup Environ Med 2010;67:154–8.

10 McDonald JC, McDonald AD, Hughes JM, et al. Mortality from lung and kidney disease in a cohort of North American industrial sandworkers: an update. Ann Occup Hyg 2005;49:367–73.

11 Cherry NM, Burgess GL, Turner S, et al. Crystalline silica and risk of lung cancer in the potteries. Occup Environ Med 1998;55:779–85.

12 Reid PJ, Sluis-Cremer GK. Mortality of white South African gold miners. Occup Environ Med 1996;53:11–16.

13 Radican L, Blair A, Stewart P, et al. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. J Occup Environ Med 2008;50:1306–19.

14 Graham WGB, Costello J, Vacek PM. Vermont granite mortality study; an update with an emphasis on lung cancer. J Occup Environ Med 2004;46:459–66.

15 Miller BG, MacCalman L. Cause-Specific mortality in British coal workers and exposure to respirable dust and quartz. Occup Environ Med 2008;65:270–70.

16 Checkoway H, Heyer NJ, Seixas NS, et al. Dose-Response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. Am J Epidemiol 1997;145:680–8.

17 Chen H, Harris J, McDonald C, et al. Mortality in a cohort of Staffordshire pottery workers: follow-up to December 2008. Occup Environ Med 2013;70:149–55.

18 Zhang X, Wang H, Zhu X, et al. Cohort mortality study in three ceramic factories in Jingdezhen in China. J Huazhong Univ Sci Technolog Med Sci 2008;29:386–90.

19 Sjögren B. Occupational exposure to dust: inflammation and ischemic heart disease. Occup Environ Med 1997;54:466–9.

20 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

21 Ofek Shlomai N, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. Eur J Clin Microbial Infect Dis 2015;34:887–97.

22 Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1–30.

23 Melsen WG, Bootsma MCJ, Rovers MM, et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123–9.

24 Palmer TM, Sterne JAC. Meta-Analysis: an updated collection from the Stata Journal. Crc Press, 2009.

25 Longnecker MP, Berlin JA, Orza MJ, et al. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1986;260:652–5.

26 Chen J, R-S et al. Respiratory disease and cardiovascular morbidity. Occup Environ Med 2005;62:650–5.

27 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;7:1773–806.

28 Park E-K, Thomas PS, Wilson D, et al. Chest pain in asbestos and silica-exposed workers. Occup Med 2011;61:178–83.

29 Kumagai N, Nishimura Y, Maeda M, et al. Immunological effects of Silica/Asbestos. Jpn. J. Hyg. 2010:65:493–9.

30 Msiska Z, Pacurari M, Mishra A, et al. Double-strand breaks by asbestos, silica, and titanium dioxide: possible biomarker of carcinogenic potential? Am J Respir Cell Mol Biol 2010;43:210–9.

31 Matsuizaki H, Kumagai-Takei N, Lee S, et al. Search for biomarkers of asbestosis exposure and asbestosis-induced cancers in investigations of the immunological effects of asbestosis. Environ Health Prev Med 2017;22:53.

32 Maeda M, Nishimura Y, Kumagai N, et al. Dysregulation of the immune system caused by silica and asbestosis. J Immunotoxicol 2010;7:268–78.

33 Verbeek J, Patiloch D, Möhner M. Effects of occupational exposure to respirable quartz dust on acute myocardial infarction. Occup Environ Med 2019;76:370–5.

34 Schins R, Borm PJ. Mechanisms and mediators in coal dust induced toxicity: a review. Ann Occup Hyg 1999;43:7–37.

35 Ekinci MSV, Sciacca RR, Boden-Alba B, et al. Relative elevation in baseline leukocyte count predicts first cerebral infarction. Neurology 2005;64:2121–5.

36 Currica I, Imboden B, Bettschart R, et al. Alpha-1 antitrypsin deficiency: from the lung to the heart? Atherosclerosis 2018;270:166–72.

37 Adelroth E, Airway inflammation in iron ore miners exposed to dust and diesel exhaust. Respir J 2006;27:714–9.

38 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.