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

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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 retroprospective studies.

Data extraction and synthesis We extracted data using a piloted 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.

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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.

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]

In 1997, Sjogren[28] published a review article on ischaemic heart disease among quartz-exposed workers. The author concludes that stonecutters, 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.[28] 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.[29] The objective was formulated using the PICOS criteria (PICOS: population: workers; intervention: exposure to silica or quartz; comparison: non-exposed silica workers or general population; outcome: heart disease; study: cohort studies).

Type of studies

We included cohort studies, including prospective, retrospective and retroprospective studies.

Search strategy

We carried out literature search in PubMed, ScienceDirect, Springer and EMBASE without language restrictions (from 1 January 1995 to 22 December 2018) using free text and keywords. The original literature search was updated on 20 June 2019. Search terms for occupational silica exposure included 'silica' as well as other related vocabulary (quartz, dust, coal, pottery, mine, sand, granite and stone). Online supplementary file 1 provides the full search strategy for PubMed, which was adapted and used to search other databases. For completeness, we also searched all references cited in the original papers and authors' other related studies.

Study population and exposure definition

The exposure of interest was silica dust, and we included studies with silica-exposed workers. In addition to the ever/never exposed inclusion criteria, some other additional characteristics of workers were included in our analyses: exposure measurement method (including cumulative exposure, qualitative exposure or mean exposure), 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/m^3-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.[7]

Study quality assessment

The Newcastle-Ottawa Quality Assessment Scale for cohort studies was used for quality assessment and one point for every satisfactory answer.[30] 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.[31] 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.[31] 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.[31] We calculated the variance estimate, I^2, as a measure of heterogeneity among studies.[32] The weight of the result was computed from the individual original estimate SE as 1/SE.[2] All statistical analyses were performed using STATA V.15.0 (metan, metabias and funnel commands).[33]

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,

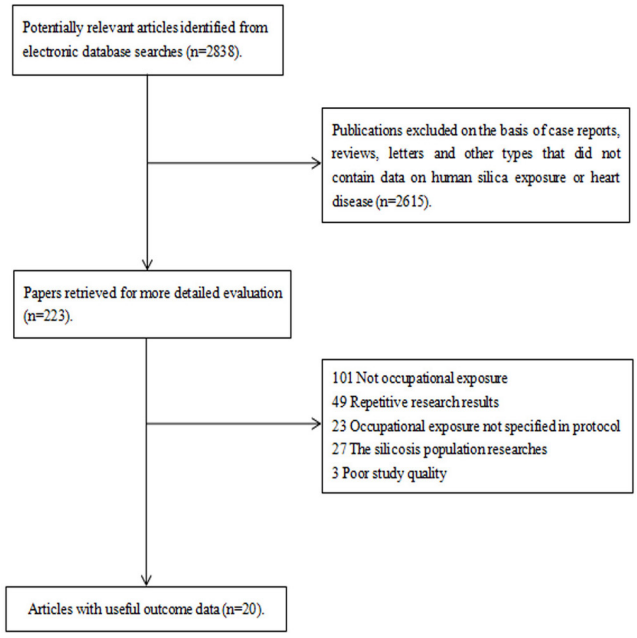

Figure 1 Flow chart of study selection for meta-analysis.

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 disease[6–10 13–23]; 5 reported on the risk of pulmonary heart disease[7 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 ≥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 o 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.[6 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)	338 100 311	Mortality 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	1962–1985 Mortality	Pulmonary heart disease (ICD-7 codes) Coronary heart disease (ICD-7 codes)	92 26	1.79 (1.35 to 2.38) 0.97 (0.61 to 1.56)
Weiner *et al* (2007)[16]	Sweden, 11 896 male mine and stone workers.	1970–1995	1970–1995 Mortality	Ischaemic 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: I00–I09) Ischaemic heart disease (ICD-10: I11) Hypertensive heart disease (ICD-10: I13) Other heart disease (ICD-10: I20–I51)	1528 496 322 500	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)[6]	China, 7665 workers (6542 male and 1123 female) in 1 iron mine company.	1960–1974	1960–2012 Mortality	Ischaemic heart disease (ICD-10: I20-I25) Pulmonary heart disease (ICD-10: I26–I27)	219 66	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 10 511 female) at 20 metal mines and 9 pottery factories.	1915–1974	1960–2003 Mortality	Pulmonary heart disease (ICD-10: I26-I27) Hypertensive heart disease (ICD-10: I11) Ischaemic heart disease (ICD-10: I20–I25) Chronic rheumatic heart disease (ICD-10: I05–I09)	2729 391 624 123	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)	384 585	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)[7]	USA, 4851 workers (4569 male and 51 female) in 18 industrial sand plants.	1960–1978	1974–1996 Mortality	Ischaemic heart disease (ICD-9: 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	Myocardial infarction (ICD-6 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)[25]	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)[26]	UK, 5115 male workers at pottery industry.	Before 1960–2008	1985–2008 Mortality	All heart diseases (ICD-9: 391–429) (ICD-10: I01–I51)	609	1.00 (0.92 to 1.08)
McDonald *et al* (2005)[19]	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)[20]	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)[21]	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)[27]	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 7and with mean exposure measurement. The statistical heterogeneity among studies could

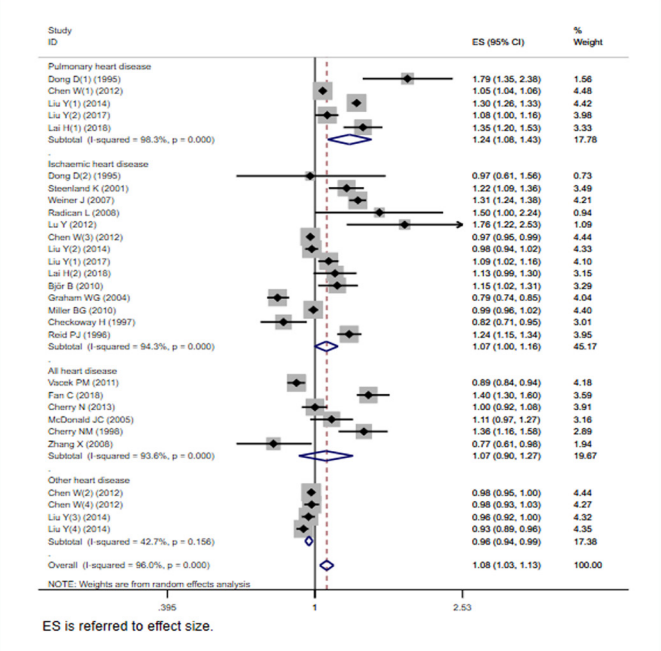

Figure 2 Forest plot of the association between occupational silica exposure and risk of heart disease. ES, effect size.

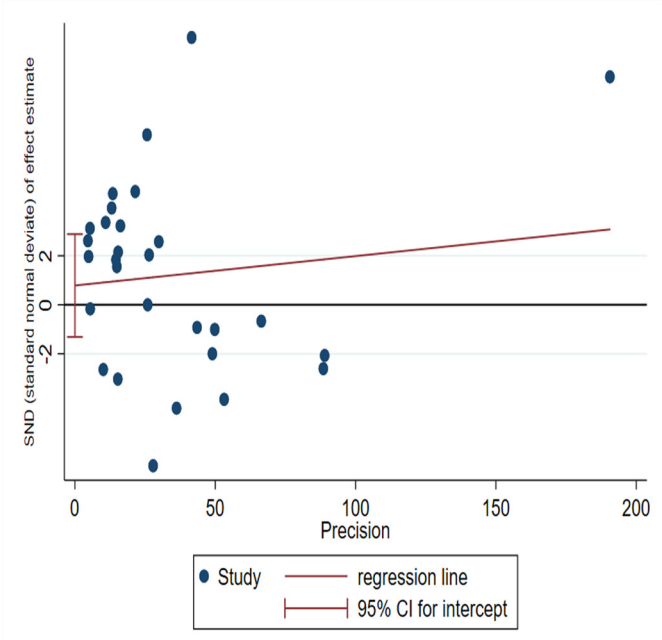

Figure 3 Egger's publication bias plot.

Table 2 Subgroup analyses of silica exposure and heart disease

Study characteristics	Category	Cohorts (n)	I^2 value (%)	P value for heterogeneity	Meta-RR (95% CI)	Tau^2
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						
	<10 000 participants	11	94.3	0.000	1.07 (0.94 to 1.22)	0.0454
	10 000–20 000 participants	5	94.8	0.000	1.24 (1.03 to 1.48)	0.0360
	>40 000 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

Table 2 Continued

Study characteristics	Category	Cohorts (n)	I^2 value (%)	P value for heterogeneity	Meta-RR (95% CI)	Tau^2
Exposure type						
	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						
	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						
	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.

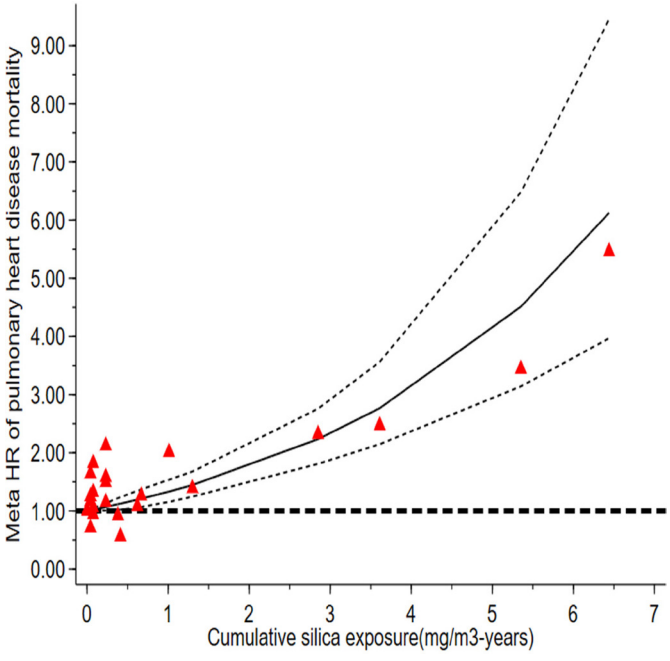

Figure 4 Exposure-response trend of pulmonary heart disease mortality with meta-HR (solid lines), 95% CI (short dashed lines) and yline=1 (thick dashed line).

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.[7 14 22 32 36] 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.[22–27] 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

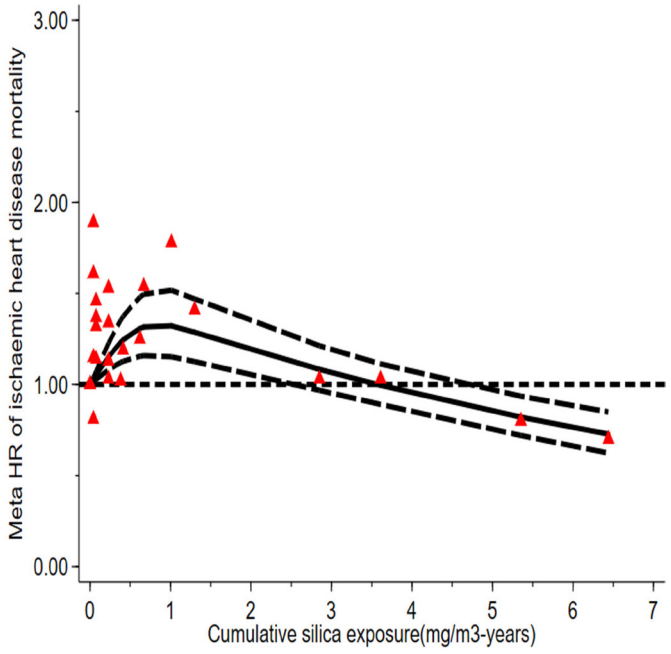

Figure 5 Exposure-response trend of ischaemic heart disease mortality with meta-HR (solid lines), 95% CI (long dashed lines) and yline=1 (thick dashed line).

healthy worker effect, which would normally cause bias towards the null.[32]

As for occupation, workplace changes related to silica forms may play an important role in affecting heart disease risk estimate. Our analysis of studies based on mine and stone foundry workers showed no significant increase in the risk of heart disease. However, Cherry *et al*[20] revealed high standardised mortality ratio of all heart diseases among pottery and sandstone workers. Particulate matter size fractions and potential interaction of silica with ambient particulate should be considered.[36–41]

Other factors, in addition to silica, may have an impact on the risk for heart disease. Silica-exposed workers who have been smoking at least one cigarette per day for at least 6 months showed a significantly increased HR of ischaemic heart disease mortality.[6] Moreover, study sample size, quality score, exposure measurement method, exposure assessment method, exposure types and research categories are important to estimate risk of heart disease.

Our exposure-response analyses revealed an excess risk of pulmonary heart disease in workers exposed to silica, but not for ischaemic heart disease. We acknowledge that substitution of open-ended lower category by the given bound divided by 1.2 might lead to overestimation of low-level exposure. However, the exact biological mechanisms underlying the non-significant dose–response association between occupational silica exposure and risk of ischaemic heart disease have not been fully understood. There is a higher likelihood that preceding respiratory disease is a competing cause of death for ischaemic heart disease.[14 35] Chronic infectious respiratory tract disease also appears to play an independent role in the development of ischaemic heart disease.[35] A case–control 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.[42] This evidence might indicate a possible dynamic link among occupational silica exposure, respiratory disease, and ischaemic heart disease and stroke.[13]

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),[43] while relative elevations in leucocyte count and A1AT deficiency are associated with increased cardiovascular risk.[44 45] Moreover, silica might induce inflammation, which plays a key role in coronary artery disease.[46 47]

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.

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