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## Review Article

## The association Between Occupational Exposure to silica and Risk of Developing Rheumatoid Arthritis: A Meta-Analysis

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is an autoimmune disease with systemic inflammatory arthritis. This meta-analysis was conducted to examine the association between occupational exposure to silica and the risk of developing RA among different workers.

**Methods:** In this meta-analysis, we searched relevant published studies using major electronic databases including Scopus, PubMed, ISI Web of Science, and Google Scholar search engine up to October 2019, and the references of retrieved articles were also checked for further possible sources. A random-effects model was used to account for heterogeneity among the results of the studies using the pooled odds ratios (ORs) and their 95% confidence intervals (CIs). The Q-statistic and I<sup>2</sup> tests were calculated to assess heterogeneity between the studies.

**Results:** The pooled calculation of OR indicated a significant association between occupational exposure to silica and risk of developing RA among different workers (OR = 2.59, 95% CI = 1.73 to 3.45). In addition, the pooled estimates of OR in smokers were statistically significant (OR = 2.49, 95% CI = 1.13 to 3.86).

**Conclusions:** The findings of the present study reveal that occupational exposure to silica may be associated with increased risk of developing RA.

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## 1. Introduction

Autoimmune diseases as a general term refer to a group of immune disorders, including scleroderma, renal disease, lupus, and rheumatoid arthritis (RA), which has been recognized in the past decade. RA is a chronic inflammatory disease characterized by symmetric polyarthritis [1]. In this chronic disease, painful inflammation of the synovial tissues of multiple joints can ultimately lead to joint destruction and disabilities. This autoimmune diseases affect approximately 0.5–1% of the population around the world. According to the findings of many previous studies, some parameters such as genetics, environmental pollutants, certain underlying diseases and their complications, types of food diet, including consumption of vitamin D

supplements and antioxidants, and consumption of alcohol are important factors in the etiology of RA [2]. There is an increase in the number of studies about the genetic role, but data regarding environmental factors that may cause RA are rare [3]. In recent years, many researchers are interested to investigate the relation between occupational exposures (e.g., silica) and risk of RA [4].

Crystalline silica is a ubiquitous mineral and a basic component of soil, sand, granite, and many other minerals. There are two kinds of silica, organic and inorganic silica. Occupational exposure to inorganic silica occurs in a large number of industries and settings, such as mines, stone quarries and granite production, ceramic and pottery industries, steel production, tunnel building, and many others [5]. Experimental studies have shown that mineral oils can

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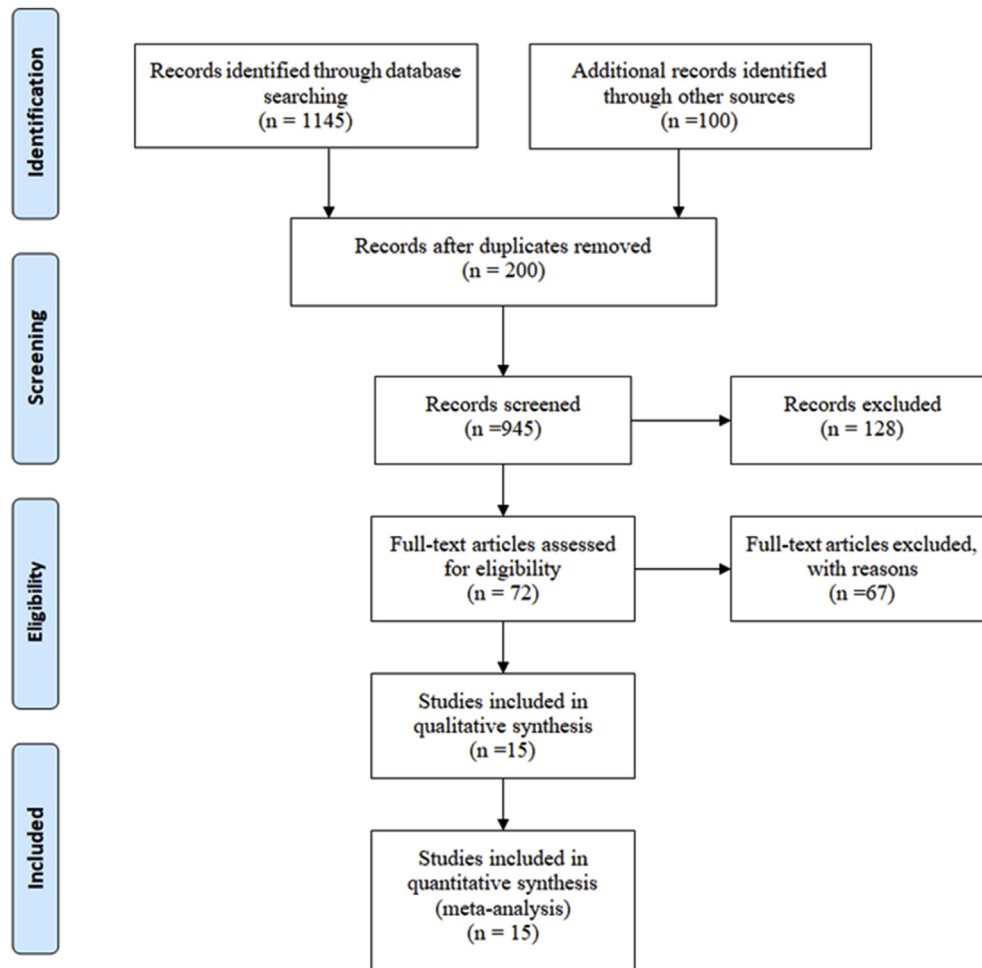


Fig. 1. Flow diagram of study selection process.

induce arthritis in animals, and it has been suggested that they may act as the so-called adjuvants enhancing immune reactions. A similar mode of action has been suggested for silica [6].

The occupational exposure to crystalline silica may generally occur all over the world via various industries such as those of construction, glass, mining, agriculture, ceramics, and electronics [7]. Studies conducted by Blanc et al. [8] on construction workers, by Vihlborg et al. [9] on iron foundry workers, and by Turner and Cherry [10] on pottery industry workers, who were exposed to silica, showed that there was a significant relationship between exposure to silica and increased risk of autoimmune disorders. In addition to silica, cigarette smoking has been documented to be an environmental risk factor, and its interaction with silica has been shown to be associated with a more severe form of RA [11–13]. Stolt et al. [14] reported that combined exposure to silica and cigarette smoking in the Swedish population was a significant risk factor in the development of RA. The association between occupational exposure to silica and the risk of developing RA has been investigated previously. Several studies showed a significant association between exposure to silica and risk of developing RA [6,15,16], whereas other studies demonstrated no association between them [10]. Therefore, this meta-analysis was conducted to pool all case-control, cross-sectional, and cohort studies in broader databases to obtain the association between occupational exposure to inorganic dusts (crystalline silica) and the risk of developing RA among different workers.

## 2. Materials and methods

### 2.1. Data sources

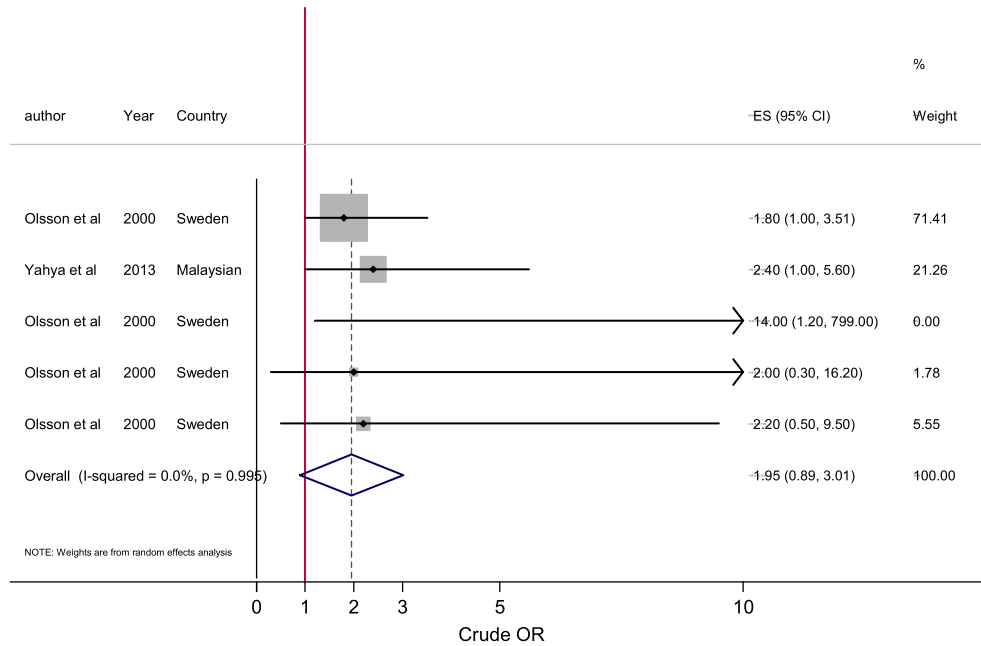
We performed a systematic review and meta-analysis study to investigate the relationship between occupational exposure to silica and the risk of developing RA. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to improve the reporting quality of the systematic review and provide transparency in the selection process of articles [17]. To select the relevant studies, a systematic search was carried out on leading databases, including ISI Web of Science, Scopus, Google Scholar search engine, and PubMed up to October 2019.

### 2.2. Search strategy

The electronic search was carried out using the following keywords: (“Arthritis rheumatoid” OR “rheumatoid arthritis”) AND (“silicon-dioxide” OR “silica” OR “silicon” OR “silic” OR “tridynite”) Filters: Humans; English.

### 2.3. Inclusion and exclusion criteria

Only manuscripts in English were included. The relevant documents in association with occupational exposure to silica and the risk of developing RA were identified, and their titles, abstracts, and



**Fig. 2.** A Forrest plot for estimated crude OR of RA for silica exposure. CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; ES, effect size.

also full texts were completely reviewed. In addition, references of the searched studies were evaluated to seek additional relevant studies and prevent missing information. In this study, cross-sectional, case–control, and cohort studies were included. Case series, case reports, review articles, letters to the editors, and also duplicate articles were excluded from this study.

#### 2.4. Identification of RA and exposure assessment

In the present study, cases of RA were defined as those subjects for whom the examining physician had responded yes to the question on RA on the last available medical examination form. In addition, assessment of occupational exposure was performed based on job title, postal questionnaire about occupational histories, telephone interview about occupational histories or using the medical record [developing anticitrullinated protein antibody (ACPA), ACPA-positive and ACPA-negative RA], and diagnoses of silicosis as a proxy for silica exposure, according to American College of Rheumatology criteria for RA.

#### 2.5. Data extraction and quality assessment

The quality of each retrieved study was independently reviewed by two authors (F.M. and S.K.), and any disagreement between the two authors was discussed to reach a consensus. In this meta-analysis, to reduce data collection errors, data extraction was performed for all eligible studies using the extraction form. In this form, information such as first author, publication's year, age (mean or range), sample size, adjustment, estimated effect size (overall and in sub-groups), and occupation was collected.

#### 2.6. Quality assessment

The quality assessment of the studies was performed by the improved Newcastle–Ottawa scale [18]. In this scale, there are three sections, including election (four items), comparability (two items), and exposure or outcomes (three items), and it ranges from 0 to 9. Two investigators conducted the quality assessment

independently, and scores of the studies were considered low quality (<7 points) and high quality ( $\geq 7$  points).

#### 2.7. Statistical analysis

The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from eligible studies using the random-effects model. The subgroup analyses were conducted based on the adjustment or crude reporting of association. The heterogeneity of results between the studies was checked using the Q value and  $I^2$  statistic [19]. The low, moderate, and high heterogeneity was considered by  $I^2$  statistic values of 25%, 50%, and 75%, respectively. The publication bias was assessed using the funnel plot as well as Begg's and Egger's tests [20]. All statistical analyses were performed at a significance level of 0.05 using Stata software version 13 (Stata Corp, College Station, TX, USA).

### 3. Results

#### 3.1. Description of the studies

A total number of 1245 studies were retrieved at the beginning of our systematic search on the mentioned databases until October 2018. We excluded 200 duplicates and 817 irrelevant topics through screening titles and abstracts. From the remaining 72 articles, 67 studies were excluded because they were letters to editors, commentaries, and reviews or they did not fulfill our inclusion criteria. Finally, 15 articles remained for the meta-analysis. Fig. 1 shows the search process. The included studies in this meta-analysis were as follows: five cohort studies [8–10,16,39], eight case control studies [14,21–25,27,28], and two cross-sectional studies [4,26]. Estimation was based on OR in 11 studies, based on risk ratio and rate ratio in three studies, and based on hazard ratio in one study. All included articles were published in English language.

#### 3.2. Main analysis

The association between occupational exposure to silica and the risk of developing RA, which was evaluated using the Forest plot,

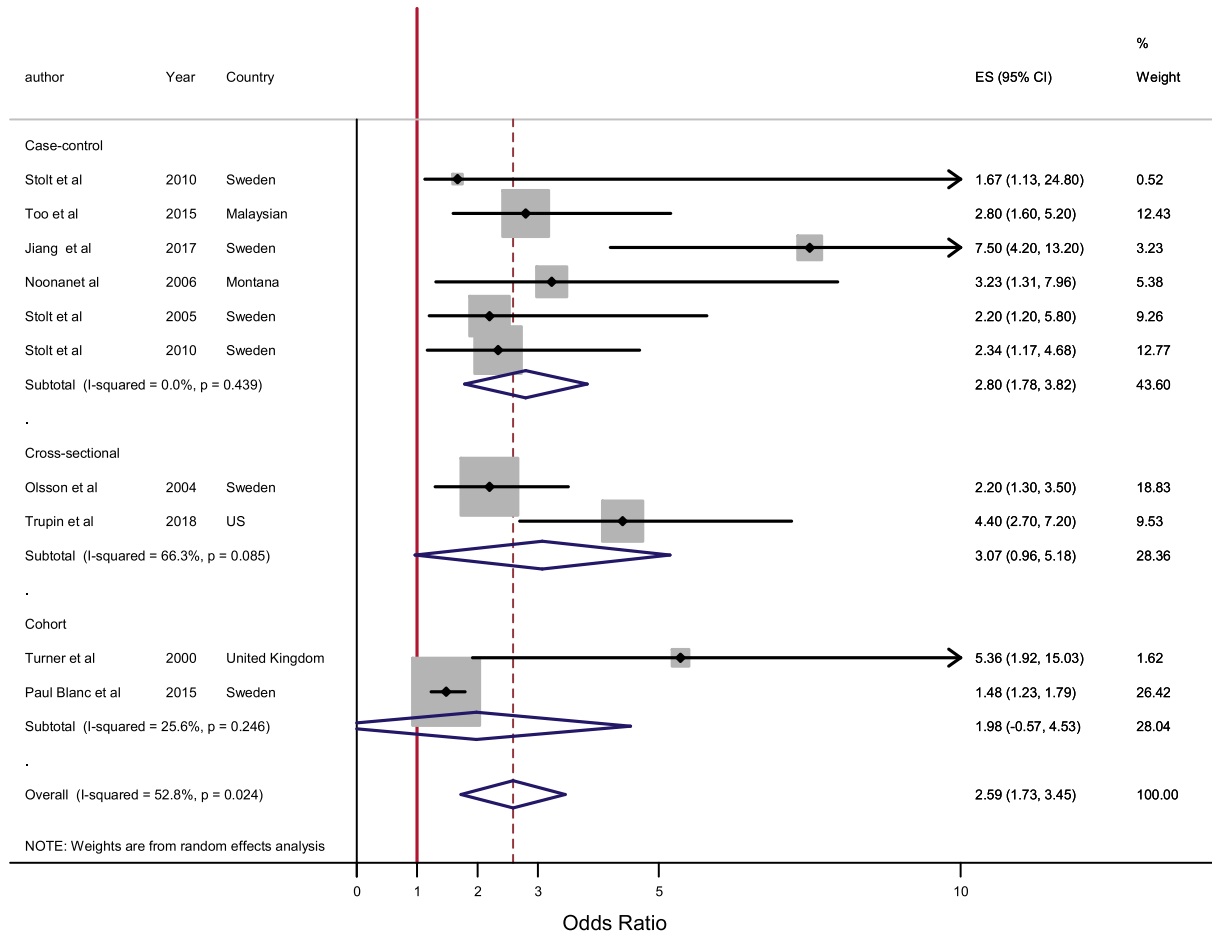


Fig. 3. A Forrest plot for estimated adjusted OR of RA for silica exposure. CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; ES, effect size.

are indicated in Fig. 2 and Fig. 3. The pooled estimates of OR were according to the crude and adjusted ORs (OR = 1.95, 95% CI = 0.89 to 3.01 and OR = 2.59, 95% CI = 1.73 to 3.45, respectively) between occupational exposure to silica and the risk of developing RA among different workers. Four studies evaluated the association between smoking occupational exposure to silica and the risk of developing RA separately based on rate ratio (RR) and hazard ratio [9,16,27,28], and all of them showed a significant association between exposure to silica and the risk of developing RA. There was moderate heterogeneity among the studies that investigated the risk of developing RA among different workers according to adjusted OR ( $I^2 = 52.8\%$ ,  $p = 0.024$ ). In addition, as shown in Fig. 5, asymmetric shape of the funnel plot indicates an evidence of the publication bias in the included studies. The  $p$  values for Begg's and Egger's regression were 0.049 and 0.057, respectively.

### 3.3. Subgroup analysis

We also separately pooled the ORs with regard to the association between exposure to silica and the risk of developing RA in studies that reported this association in smokers. As shown in Fig. 4, the pooled estimates of OR in smokers were statistically significant (OR = 2.49, 95% CI = 1.13 to 3.86).

### 3.4. Quality of the studies

Three of the included studies in the present meta-analysis were of low quality, and others were of high quality according to the Newcastle–Ottawa scale (Table 1).

## 4. Discussion

In this systematic review, we evaluated the association between occupational exposure to silica and the risk of developing RA in different workers. The findings obtained from this study are important and useful in implementing different programs for the prevention of development of RA among health workers. In this meta-analysis, the association between occupational exposure to silica and the risk of developing RA was evaluated among various workers using all case–control, cross-sectional, and cohort studies that were evaluated and conducted up to now. The results of the present study were similar to the results of ten included studies, which showed that there was a significant association between occupational exposure to silica and the risk of developing RA among various workers. The reports of the pooled estimate and heterogeneity among the included studies showed that the obtained OR was 2.59 (moderate heterogeneity). Among the previous related studies, up to now, only one meta-analysis has been performed on the association between exposure to silica and the risk of developing RA. Khuder et al. [29] investigated the association between exposure to silica and increased mortality rate due to developing RA among workers (RR = 3.43, 95% CI = 2.22 to 5.22). Ten studies were included in this meta-analysis, in which the electronic search was limited to the MEDLINE database. In addition, the previous relevant studies were those that had been conducted until 2000, whereas in the current meta-analysis, in addition to PubMed, we searched ISI Web of Science, Scopus, and Google scholar databases up to October 2019 and included 15 studies. The results of the studies by Pollard [30] and Vihlborg et al. [9] showed

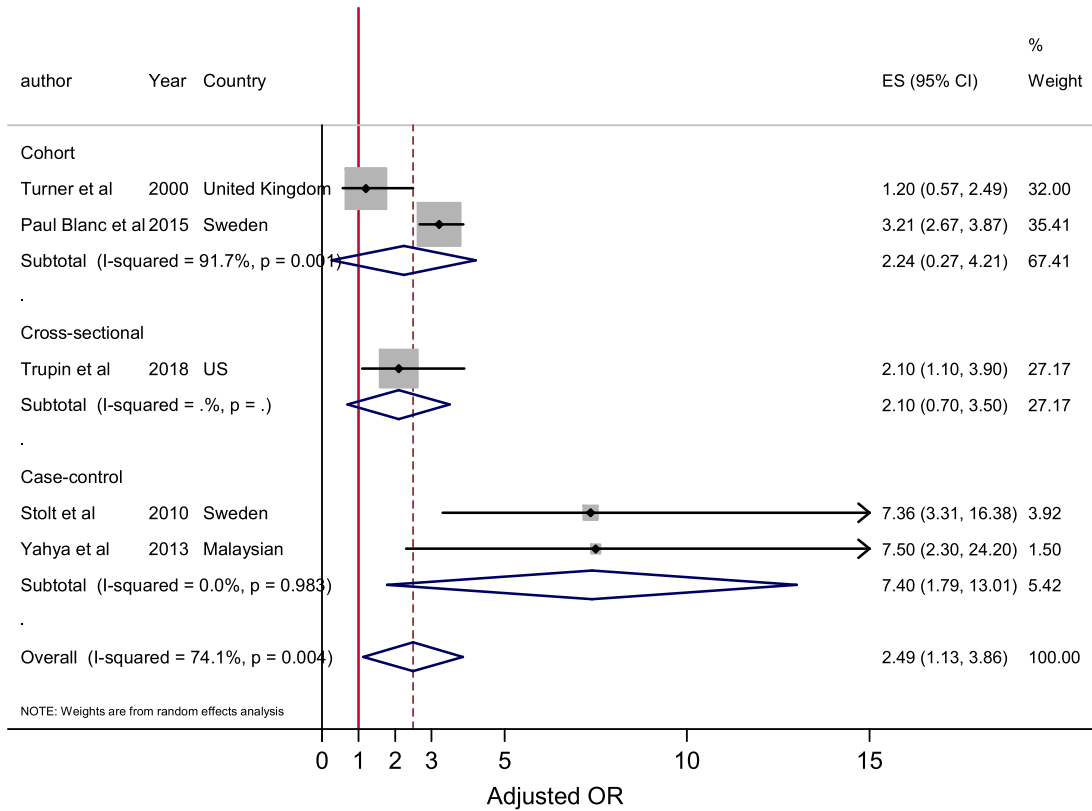


Fig. 4. A Forrest plot for estimated adjusted OR of RA for silica exposure in smokers. CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; ES, effect size.

that environmental factors have an important role in the development of RA. These factors included food, fluids, air pollution, chemical compounds, kind of infections, by-products obtained from different processes, radiation, and occupational and environmental exposure to silica [31,32]. Although epidemiological studies showed that exposure to silica can increase risk of developing RA, the exact mechanism of silica that may lead to development of RA is not clear. Possible mechanism that was suggested by various studies is stimulation of the immune system. Silica is a selective toxin for macrophages that binds to their cell membrane and causes disturbance in T lymphocyte–macrophage immune regulation and can lead to secretion of inflammatory factors that are responsible for stimulating DNA synthesis in synovial cells [33]. In addition to exposure to silica by various industries and mines,

lifestyle, genetic factors, alcohol consumption, and cigarette smoking have been investigated in recent studies [15,34,35]. In our meta-analysis, association between exposure to silica and risk of developing RA in smoking workers was significant because cigarette smoke contains more than 4,000 chemicals that are very toxic or carcinogenic. The metabolism of this component in the body is performed by (Phase I and Phase II) enzymes in the liver that play a critical role in decreasing oxidative stress and toxicity of smoking in the body [36]. Despite multiple reports indicating relationship between smoking and exposure to silica and risk of developing RA, it depends on various factors such as second-hand or passive exposure to smoking and also degree of heavy and low exposures to silica in different jobs, such as rock drilling, stone crushing, and stone dust [22]. Few studies have investigated the association between amount and dose of silica or duration of exposure to silica and development of RA. Several studies showed that there was a significant association between risk of development of RA and cigarette smoking [16,37]. The results of the study conducted by Zeng [37] showed a significant relationship between exposure to silica and smoking and development of RA among the Swedish population; the results of the study also indicated that the effects of cumulative dose and duration of smoking in development of RA can remain after 10 years of smoking cessation. In other study performed by Karlson et al. [38], they showed that there was a dose–risk relationship between cigarette smoking and the risk of developing RA and this risk was higher in workers with heavy smoking and longer duration. Therefore, according to the results of several previous studies and the present study, there was a relationship between smoking and exposure to silica and risk of developing RA [37].

The present meta-analysis has two limitations: first, there was no specific categorization for occupations, and we could not have subgroup analysis according to different occupations. Second,

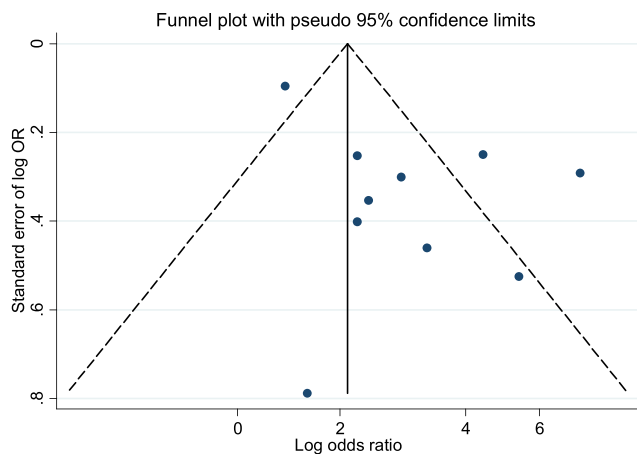


Fig. 5. Funnel plot of included studies in the meta-analysis. OR, odds ratio.

**Table 1**  
Characteristics of the studies used for meta-analysis.

1 <sup>st</sup> author, year	Reference number	Country	Design	Sample	Age (years)	Estimate	Quality	HR/OR/RR (95% CI) in subgroups	Exposure assessment	Duration of exposure	Occupation
Paul Blanc et al. (2016)	[8]	Sweden	Cohort	2551 (30 RA cases)	—	HR	High	Overall: 1.57 (1.2–2.06)	Occupational histories or using the medical record	9 years	Foundry workers with exposure for >7.5 years
Paul D. Blanc et al. (2015)	[16]	Sweden	Cohort	240,983 (713 RA cases)	30–84	AOR	High	Overall: 1.39 (1.17–1.64) Smokers: 1.36 (1.11–1.68)	Occupational histories or using the medical record	13 years	Construction workers
Jiang et al. (2017)	[22]	Sweden	CC	599	—	AOR	High	Overall: 7.5 (4.2–13.2)	Medical record [antititrullinated protein antibody (ACPA)-positive RA]	12–19 years	Swedish Epidemiological Investigation of RA project
Klockars et al. (1987)	[27]	Finland	Cohort	1026	15–72	RR	High	Overall: 5.08 (3.31–7.79)	Medical record [sarcoidosis and seropositive rheumatoid arthritis (RA)]	12 years	Granite workers
Olsson et al. (2004)	[4]	Sweden	CS	2204 control, 715 cases	16–75	AOR	Low	Overall: 2.2 (1.3–3.5)	Postal questionnaire about occupational histories	6 months	Farmers and farm workers
Stolt et al. (2005)	[24]	Sweden	CC	276 control, 276 cases	18–70	AOR	High	18–70 years: 2.2 (1.2–3.9) >70 years: 2.7 (1.2–5.8)	Criteria of the American College of Rheumatology (ACR)	5 years	Worked with rock drilling or stone crushing
Yahya et al. (2013)	[28]	Malaysian	CC	213 control, 149 cases	18–70	COR	High	Overall: 2.4 (1.0–5.6) Smokers: 7.5 (2.3–24.2)	Medical record (ACPA-positive RA)	4 years	Occupational exposure to rock drilling, stone crushing
Stolt et al. (2010)	[14]	Sweden	CC	659 control, 577 cases	18–70	AOR	High	Stone dust: 1.67 (1.13–2.48) Rock drilling: 2.34 (1.17–4.68) Smokers: 7.36 (3.31–16.38)	Criteria of the ACR for RA	10 years	Exposure to stone dust, rock drilling
Too et al. (2015)	[21]	Malaysian	CC	910 control, 910 cases	18–70	AOR	High	Overall: 2.8 (1.6–5.2)	Medical record (developing ACPA- positive and ACPA-negative RA)	1–4 years	Textile dust workers
Trupin et al. (2018)	[26]	US	CS	973	66 ± 10	AOR	High	Overall: 4.4 (2.7, 7.2) Smokers: 2.1 (1.1, 3.9)	Telephone interview about occupational histories		Coal mining
Turner et al. (2000)	[10]	United Kingdom	Cohort	8325 (58 RA cases)	—	COR	Low	Overall: 5.36 (1.92–15.03) Smokers: 1.2 (0.57–2.49)	Occupational histories or using the medical record	4.4 and 5.6 years	Coal mining
Vihlborg et al. (2017)	[9]	Swedish	Cohort	2187	20–45	RR	High	Overall: 1.7 (1.01–2.69)	Medical record [sarcoidosis and seropositive rheumatoid arthritis (RA)]	NM	Workers in Swedish iron foundries
Noonan et al. (2006)	[23]	Montana	CC	387 control, 129 cases	≥65	AOR	Low	Overall: 3.23 (1.31–7.96)	Occupational histories or using the medical record	At least 6 months	Occupational and environmental exposure to asbestos-contaminated vermiculite
Olsson et al. (2000)	[25]	Sweden	CC	859 control, 422 cases	25–75	COR	High	Farmers: 1.8 (1.0–3.51) Textile workers: 2.0 (0.3–16.2) Asphalts: 14.0 (1.2–799.0) Service stations: 2.2 (0.5–9.5)	Postal questionnaire about occupational histories	27 months	Workers of textile asphalts and service stations and farmers
Steenland et al. (1995)	[39]	US	Cohort	3328	—	RR	High	Overall: 2.19 (1.27–3.50)	NM	NM	Gold miners

AOR, adjusted OR; CC, case-control; CI, confidence interval; CS, cross-sectional; COR, crude OR; HR, hazard ratio; OR, odds ratio; RA, rheumatoid arthritis; NM, not mentioned; RR, rate ratio.



baseline characteristics in the included studies such as duration of exposure, age-group, and so on were substantially different and imposed residual confounding to the results.

## 5. Conclusions

Investigations regarding exposure to silica or risk of developing RA are sufficient, but few studies have paid much attention to their relationship. The results of pooled effects analysis on fifteen studies in the present study indicate a significant association between exposure to silica and risk of developing RA. These findings can provide a new and useful approach for the prevention of developing RA in workers exposed to silica in different occupational environments.

## Ethical approval

This study does not contain any studies with human participants or animals performed by any of the authors.

## Conflicts of interest

The authors have no conflict of interest to declare.

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