

Systematic review and meta analysis

Systematic review and meta-analysis of epidemiological studies on the association of occupational exposure to free crystalline silica and systemic lupus erythematosus

Alberto Morotti ¹, Irena Sollaku¹, Simona Catalani,¹ Franco Franceschini², Ilaria Cavazzana³, Micaela Fredi², Emma Sala⁴ and Giuseppe De Palma ^{1,4}

Abstract

Objectives. Some evidence suggests that exposure to free crystalline silica may contribute to the risk of developing SLE. A systematic search was carried out for all published epidemiological studies concerning this association. A meta-analysis was conducted on relevant studies.

Methods. We searched PubMed and EMBASE databases for original articles published from 1960 to November 2019 in any language. In addition, we also searched the reference lists of included studies manually for additional relevant articles. Finally, seven studies were included in the systematic review and six studies in the meta-analysis (four case–control and two cohort studies). The odds ratio and 95% CI were calculated using a random effect meta-analysis.

Results. The meta-analysis of the studies, applying a random effect model, yielded an overall odds ratio of 3.49 (95% CI, 1.24, 9.83), with $I^2 = 92.36\%$ (pronounced heterogeneity). We also stratified the meta-analysis by study design; case–control studies: odds ratio 1.85 (95% CI, 0.96, 3.59) with $I^2 = 75.92\%$; and cohort studies (cases with silicosis): odds ratio 9.71 (95% CI, 1.13, 83.58) with $I^2 = 72.65\%$.

Conclusions. The obtained results support the hypothesis of a possible association between occupational exposure to free crystalline silica and SLE, in particular at higher exposure levels, known to induce silicosis. The studies that have investigated this association are still scarce and the heterogeneity between the studies remains high. New studies are deemed necessary to confirm the association.

Key words: SLE, lupus, free crystalline silica, silica, meta-analysis

Rheumatology key messages

- The association between occupational exposure to free crystalline silica and SLE development is still epidemiologically weak.
- Further studies in the field are needed to support, or to not support, such association.

¹Unit of Occupational Health, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health (DSMC), University of Brescia, ²Rheumatology and Clinical Immunology Unit, ASST Spedali Civili, Department of Clinical and Experimental Sciences (DSCS), University of Brescia, ³Unit of Rheumatology and Clinical Immunology, and ⁴Unit of Occupational Health, Hygiene, Toxicology and Occupational Prevention, ASST Spedali Civili di Brescia, Brescia, Italy

Submitted 9 April 2020; accepted: 17 June 2020

Correspondence to: Giuseppe De Palma, Università degli Studi di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Unit of Occupational Health, Piazzale Spedali Civili 1, Brescia 25121, Italy. E-mail: giuseppe.depalma@unibs.it

Introduction

SLE is a chronic, systemic autoimmune disease characterized by autoantibody production, complement activation, immune complex deposition and other immune processes [1, 2]. The disease has a multisystem involvement: articular, cutaneous and mucous, renal, haematological, neurological, pulmonary and cardiovascular. The clinical characteristics of silica-associated SLE subjects compared with non-silica-SLE subjects have not been much investigated and epidemiological studies have not

focused on this. Although the presence of lung impairment is very often found in silica-associated SLE subjects [3] and the lung might be a site of specific involvement of SLE, this remains only a speculation without foundation.

The SLE diagnostic criteria have changed over the years, the most recent being those defined by the ACR and EULAR support in 2019 [4–6]. SLE has a reported prevalence rate in the USA of 20–150 cases per 100 000, with a predominance among women [7]. In women, the prevalence varies discretely according to ethnic group: 164 (white) to 406 (African-American) per 100 000 [8]. Recent epidemiological studies based on four American registries have shown an increase in the incidence of SLE in certain population groups such as ‘black’, ‘Asian’ and ‘Hispanic’ [9, 10].

The aetiology of SLE remains unknown and it is considered a multifactorial disorder. Many studies highlight the role of cigarette smoking, oral contraceptives and postmenopausal hormone therapies in increasing the risk, whereas moderate alcohol consumption has been shown to play a protective role [11]. Among occupational risk factors, the association with organochlorine pesticides and solvents is supported by experimental data [12]. Several studies have investigated the association between occupational exposure to free crystalline silica (FCS) and autoimmune rheumatic diseases but, among these, SLE is far less investigated. Recent experimental studies [13–15] investigating the effects of FCS on immune cells, show that chronic *in vitro* exposure to FCS can activate T responder lymphocytes and reduce regulatory T lymphocytes, with the result of making individuals more susceptible to developing autoimmune disorders [16]. In silicosis patients, chronic T cell responder activation can be related to resistance to apoptosis induced by the CD95/Fas receptor [16]. On the other hand, overexpression of the same receptor in regulatory T cells causes their apoptosis. It is hypothesized that the resulting lymphocyte imbalance may be the mechanism underlying the autoimmune response responsible for SLE. Once the autoimmune alterations occur, a pathological status is established that constantly and unstopably worsens until the appearance of the disease [16].

The main aim of this review is to evaluate all available epidemiological evidence on the relationship between occupational exposure to FCS and SLE.

Methods

We adopted the preferred reporting items for systematic reviews and meta-analysis-statement as a reporting item of our systematic review and meta-analysis [17]. The preferred reporting items for systematic reviews and meta-analysis checklist can be found in the [supplementary material](#), available at *Rheumatology* online. We defined an *a priori* protocol, and established inclusion and exclusion criteria of epidemiological studies. Inclusion criteria were studies investigating the association between occupational exposure to FCS and SLE

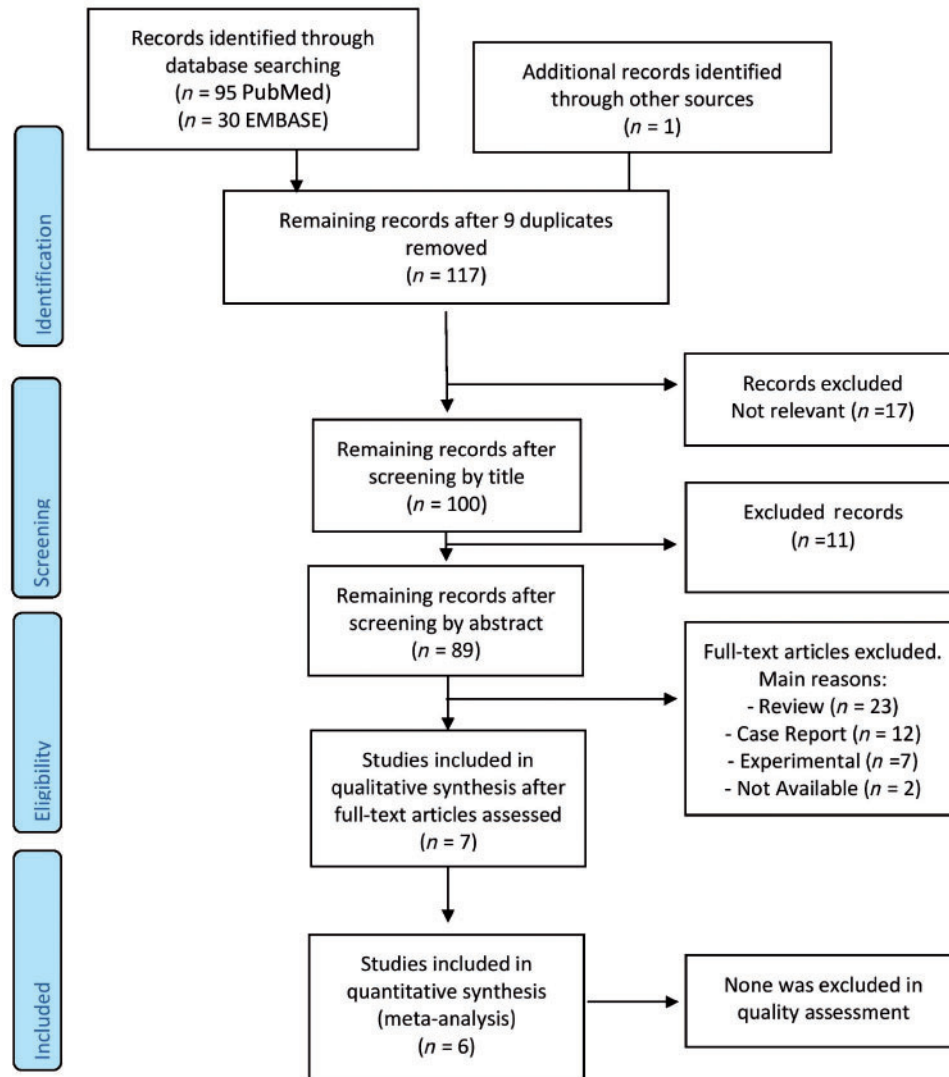
and studies in which a measure of association such as relative risk, odds ratio (OR), standardized mortality ratios or standardized incidence ratios was either reported or could be derived from data reported in the article. Exclusion criteria were by study design: experimental studies, case reports and reviews, data incompleteness (e.g. presence of prevalence data in only one of the two samples), use of data from samples of subjects already used in previous studies (in order to avoid duplication of results), use of non-standardized methods for diagnosis and/or very high risk of inaccuracy in the assessment, and inadequacy of results for meta-analysis purposes. Duplicate or irrelevant studies as well as studies with insufficient relative risk and CI data were excluded.

We searched EMBASE and PubMed for original articles published between 1960 and November 2019. The bibliographic search was extended also using the links ‘related article’ of PubMed and the reference lists of some key studies. There were no restrictions regarding the language of the articles. We performed the following literature search on PubMed, starting from the strings proposed by Mattioli *et al.* [18] (occupational diseases [MH] OR [...]) and those from the University of Texas School of Public Health Library [19] (‘case-control studies’ [Mesh: noexp] [...] cohort studies [mesh: noexp] [...]) and applying the search filter ‘silica’ to the string: (cohort studies [mesh: noexp] OR followup studies [mesh: noexp] OR prospective studies [mesh: noexp] OR retrospective studies [mesh: noexp] OR cohort [TIAB] OR prospective [TIAB] OR retrospective [TIAB] OR ‘case-control studies’ [Mesh: noexp] OR ‘retrospective studies’ [mesh: noexp] OR ‘control groups’ [Mesh: noexp] OR (case [TIAB] AND control [TIAB]) OR (cases [TIAB] AND controls [TIAB]) OR (cases [TIAB] AND controlled [TIAB]) OR (case [TIAB] AND comparison* [TIAB]) OR (cases [TIAB] AND comparison* [TIAB]) OR ‘control group’ [TIAB] OR ‘control groups’ [TIAB] OR occupational diseases [MH] OR occupational exposure [MH] OR occupational exposure* [TW] OR ‘occupational health’ OR ‘occupational medicine’ OR work-related OR working environment [TW] OR at work [TW] OR work environment [TW] OR occupations [MH] OR work [MH] OR workplace* [TW] OR workload OR occupation* OR worke* OR work place* [TW] OR work site* [TW] OR job* [TW] OR occupational groups [MH] OR employment OR worksite* OR industry) AND (‘systemic lupus erythematosus’ OR lupus).

Moreover, on EMBASE, we performed the following additional literature search: (‘systemic lupus erythematosus’/exp OR ‘systemic lupus erythematosus’ OR ‘lupus’/exp OR lupus) AND (‘silica’/exp OR silica) AND (‘case control study’/de OR ‘cohort analysis’/de OR ‘observational study’/de OR ‘prospective study’/de OR ‘retrospective study’/de).

Two authors (A.M., I.S.) independently reviewed the studies, taking into account the inclusion and exclusion criteria. Doubtful cases or disagreement situations were resolved involving a third author (S.C.).

Fig. 1 Flow chart of search and selection of studies included in the review and meta-analysis



The final selection of the included articles underwent careful reading and analysis of the entire texts.

The whole process followed during the systematic review is shown in Fig. 1. The flow chart is based on model proposed on the official preferred reporting items for systematic reviews and meta-analysis website [20]. The bibliographic search gave rise to 125 articles; a further article [21] was identified as it was cited in an included study.

Following the title revision, we eliminated 17 articles and a further 11 after abstract revision. Additional articles (23 reviews, 12 case reports, 7 experimental and 2 not available) were excluded after reading the full text, for lack of compliance with the inclusion criteria.

Finally, the studies included in qualitative synthesis were seven, six being eligible for the meta-analysis.

Data extraction

In order to perform the meta-analysis, we extracted the most relevant data from each study (Table 1), including sector of exposure, exposure assessment, number of cases and effect size (95% CI).

The quality of the studies was evaluated by applying the Newcastle–Ottawa Scale (NOS) [23], available in the supplementary material, available at *Rheumatology* online. Total final quality scores of individual studies are summarized in Table 2.

Data synthesis

The data were analysed using the Comprehensive Meta-analysis v3.0 software from Biostat Inc. (Englewood, NJ, USA) [24].

TABLE 1 SLE studies included in the systematic review and meta-analysis (except study ID 6)

| Study ID | Author | Year | Country | Year | Design | Sectors of exposure | Exposure assessment | No. of observed cases | Effect size (95% CI) |
|----------|-----------------------------|------|----------------|-----------|------------------------------------|---|--|--|------------------------|
| 1 | Makol <i>et al.</i> [28] | 2011 | USA | 1985–2006 | CO | Various including foundry work and sandblasting | Telephone interview (if the individual was deceased, a next-of-kin was interviewed). Medical records, radiographs, laboratory data were also collected | 1022 cases diagnosed with silicosis (only for the outcome: 1 case of SLE) | RR 2.53 (0.3, 21.64) |
| 2 | Cooper <i>et al.</i> [25] | 2010 | Canada | 2010 | CC | Construction or demolition jobs and others not clearly specified | Telephone interview (checklist included 16 silica-related jobs). Classification of exposure based on an algorithm | 258 cases/263 controls (only for the outcome: 40 cases/27 controls) | OR 1.6 (0.90, 2.7) |
| 3 | Gold <i>et al.</i> [21] | 2007 | USA | 1984–99 | CC, mortality–death certifies data | Among 509 different jobs: mainly hand painting, hand coating and hand decorating occupations | JEMs | 7153 cases/260 632 controls (only for the outcome: 529 cases/260 632 controls) | OR 1.02 (0.92, 1.12) |
| 4 | Finckh <i>et al.</i> [26] | 2006 | USA | 2006 | CC | Dental mechanics, construction, demolition or custodian using scouring powders | In-person interview (checklist included 15 FCS-related jobs). Exposure assessment by two reviewers using algorithms | 95 cases/191 controls | OR 4.9 (1.1, 21.9) |
| 5 | Parks <i>et al.</i> [27] | 2002 | USA | 1992–99 | CC | Dusty trades and farming (mining, sandblasting, quarrying, foundries and metal works) | In-person interview. Industrial hygienists assigned each job a level of average exposure intensity (high, moderate, low or no) | 265 cases/355 controls (only for the outcome: 13 cases of SLE) | OR 4.6 (1.4, 15.4) |
| 6 | Rosenman <i>et al.</i> [29] | 1999 | USA | 1985–96 | CO | Various including foundry work and sandblasting | Telephone interview (if the individual was deceased, a next-of-kin was interviewed). Medical records, radiographs, laboratory data were also collected | 583 cases (only for the outcome: 1 case of SLE) | RR 11.37 (0.15, 63.23) |
| 7 | Brown <i>et al.</i> [30] | 1997 | Sweden-Denmark | 1965–83 | CO, mortality–death certifies data | A review of Swedish computerized hospital diagnoses with diagnostic codes for both silicosis and SLE. The type of exposure was not better specified | A review of Swedish computerized hospital diagnoses with diagnostic codes for both silicosis and SLE. The exposure assessment was not better specified | 57 cases (only for the outcome: 8 cases of SLE) | RR 23.8 (10.3, 47) |

CC: case control; CO: cohort study; FCS: free crystalline silica; JEM: job-exposure matrix; OR: odds ratio; RR: relative risk.

TABLE 2 Quality of studies based on the Newcastle–Ottawa Scale

| Case-control studies | | | | | | | | | | |
|----------------------------------|--|-------------------------------------|---------------------------|--|--|-----------------------|---|----------------------------------|----------|--|
| Study | Selection | | | | | Comparability | | | Exposure | |
| | Is the case definition adequate? | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Exposure assessment | Same method of ascertainment for cases and controls | Non-response rate | Score | |
| Cooper <i>et al.</i> , 2010 [25] | * | * | * | * | ** | — | * | — | 7 | |
| Gold <i>et al.</i> , 2007 [21] | — | — | * | * | — | — | * | — | 3 | |
| Finckh <i>et al.</i> , 2006 [26] | * | * | * | * | * | * | * | — | 7 | |
| Parks <i>et al.</i> , 2002 [27] | * | * | * | * | ** | * | * | — | 8 | |
| Cohort studies | | | | | | | | | | |
| Study | Selection | | | Comparability | | Outcome | | | 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 the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur? | Adequacy of follow-up of cohorts | | |
| Makol <i>et al.</i> , 2011 [28] | * | * | * | * | — | * | * | * | 7 | |
| Brown <i>et al.</i> , 1997 [30] | — | — | * | — | — | * | — | — | 2 | |

***: positively evaluated items (1 = 1; ** = 2), according to the Newcastle-Ottawa scale, —: not evaluable items.

Fig. 2 Forest plot of included studies in meta-analysis, stratified by study design

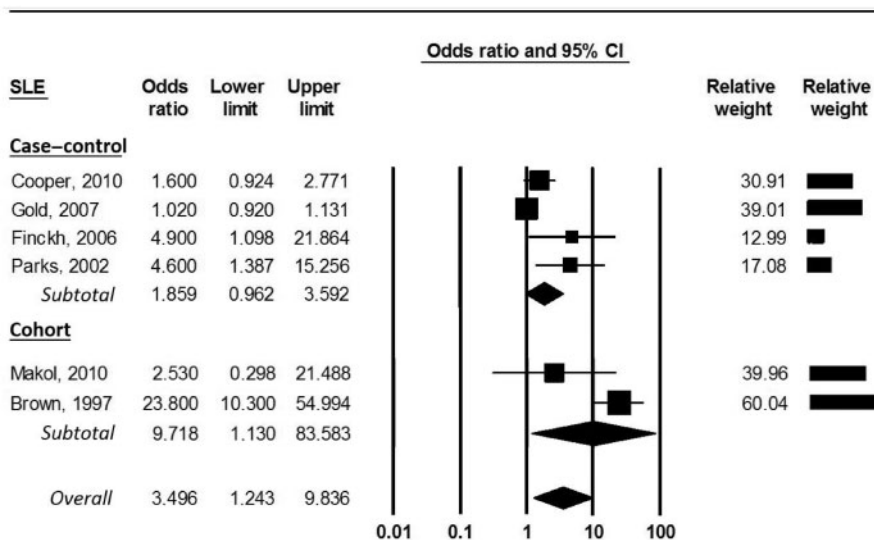
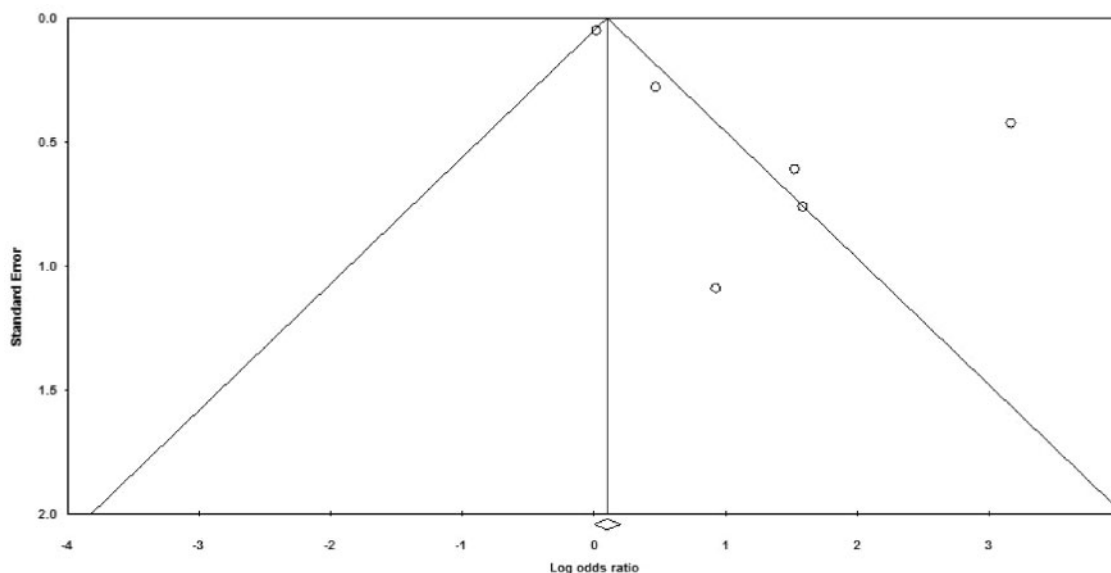


Fig. 3 Funnel plot of the meta-analysis of published studies



We chose to use the random effect model for the aggregate estimation of the association rather than the fixed effect model according to the hypothesis that it was likely to assume a high level of variability among studies. Heterogeneity among studies was assessed using the I^2 index. Heterogeneity was considered low if I^2 values were between 25% and 50%, moderate if between 50% and 75% and high if higher than 75% [25].

A funnel plot was used to identify and estimate the amount of publication bias, and the statistical evaluation was carried out by Egger's test.

Results

Search results

After an accurate procedure of selection and evaluation of 126 studies, seven were deemed relevant (Table 1):

four case-control studies [21, 26–28] and three cohort studies [22,29,30].

Study characteristics

Population

In three case-control studies [26–28], diagnosis was formulated according to the ACR diagnostic criteria. In a case-control mortality study [21], subjects were identified through the specific ICD-9 code (710.0) in their respective death certificates. In two further studies [22, 29], the information to evaluate whether patients met the ACR diagnostic criteria was insufficient. In the Brown *et al.* [30] study, the diagnosis of SLE was based on diagnostic codes reported in the medical records. Rosenman *et al.* [29] included in the analysis only individuals with a diagnosis of silicosis meeting the NIOSH criteria. According to the disease epidemiology, in every study, the sample is represented mostly by females.

Exposure assessment

Most of the investigated samples worked in dusty trades (exposure to FCS). Parks *et al.* [28] also investigated farm workers. Retrospective cohort studies on silicosis patients [22,29,30] do not provide accurate data on exposure levels.

Controls

Subjects were randomly selected and frequency-matched to the cases by the main variables, such as age, race, sex and geography.

Outcome

May FCS exposure be a significant risk factor for the development of SLE [26–28]? Are silicosis patients prone to a higher prevalence of SLE [22,29,30]? May the SLE mortality rate possibly be related to FCS exposure [21]? The methodology used by the case-control studies (one excluded [21]) was rather homogeneous. Two studies [27, 28] focused on occupational exposure to FCS, whereas the remaining considered also other risk factors. The studies were published between 1997 and 2010. In these studies, occupational exposure to FCS occurred in a variety of sectors falling under the term ‘dusty trades’ (e.g. construction, foundries, sandblasting).

Retrospective cohort studies, on the other hand, investigated the risk of developing SLE among individuals with a diagnosis of silicosis [22,29,30], which is a work-related disease tightly linked to occupational exposure to FCS.

The examined populations in the case-control studies were predominantly women: 100% [27], 90% [26, 28] and 82% [21]. In the first two studies [27, 28], there was a prevalence of African-Americans (respectively 84% and 60% of cases), as compared with the last two studies [21, 26] where the population was predominantly white-American (72% and 82%). In Makol *et al.* [22] and Rosenman *et al.* [29] the prevalence of African-Americans was 47.7%. In both studies, males predominate.

Risk of bias within studies

The quality and risk of bias appraisal was conducted using the NOS [23] by two independent evaluators (A.M., I.S.). We used a modified version of the tool in order to better adapt it to the studies we reviewed (see [supplementary material](#), available at *Rheumatology* online).

An overview of the risk of bias for each of the selected studies is shown in [Table 2](#)

The NOS produced final scores of 8 [28], 7 [27], 7 [26], 7 [22], 3 [21] and 2 [30]. The first four studies obtained similar and consistent scores, but some common critical intrinsic limiting issues emerged, such as the use of self-reported exposure information rather than objective measurements.

In the Cooper *et al.* [26] study, exposure data were collected by telephone interviews using a checklist of 16 FCS-related jobs. A similar approach was used by Finckh *et al.* [27], who used a checklist of 15 FCS-related jobs but administered by face-to-face interviews, as did Parks *et al.* [28]. A telephone questionnaire was administered to confirm the diagnosis of silicosis in two further studies [22, 29]. When interview was not possible, the questionnaire was completed drawing information from medical records. A reliable diagnosis of silicosis was based on a positive history of exposure to silica and X-ray images.

In any case, exposure information was collected decades after diagnosis and this might have caused some inaccuracies. Moreover, SLE patients might be more likely than controls to recall FCS exposure (recall bias). The exposure assessment might have been particularly inaccurate in the studies based on death certificates [20]. In two studies, a qualitative FCS exposure assessment such as ‘probable, possible, unlikely’ [27] or ‘high, moderate, low, no’ [28] was adopted. For our purposes, we decided to extract the OR corresponding to the highest exposure classes.

In the case-control studies, cases were diagnosed according to the ACR diagnostic criteria, whereas in the mortality study [20], information about diagnostic criteria was missing. In cohort studies, based on the review of medical records and/or questionnaires, there was often insufficient information to determine whether patients met the ACR diagnostic criteria.

The Finckh *et al.* [27] study was conducted only on female cases and controls residing in the same high-prevalence African-American neighbourhood.

All studies except one [30] were adjusted for the main and potential confounding agents (age, gender, geographical area, educational level). All except two studies [21, 30] were also adjusted for smoking.

Results of individual studies (meta-analysis)

In the meta-analysis, we combined the results of four case-control studies and two cohort studies using a random effect model. The results of the main meta-analysis are reported in [Fig. 2](#). The relative weights of

case-control studies are set between 12.99% [27] and 39.01% [21] and between 39.96% [22] and 60.04 [30] for cohort studies. The risk indices of the individual studies are all greater than 1, in a range starting from an OR of 1.02 (95% CI, 0.92, 1.13) [21] to a relative risk of 23.80 (95% CI, 10.30, 54.99) [30]. The study by Makol *et al.* [22] has a clearly wider CI than the others, owing to the small sample size, and therefore its relative weight was reduced, as its contribution to the final OR of the meta-analysis. The study by Brown *et al.* [30] was performed on subjects with previous past massive exposure to FCS (silicosis); in Fig. 2 the CI has clearly shifted to the right (95% CI, 10.30, 54.99).

Synthesis of results

Primary meta-analysis results

The meta-analysis of the six studies, applying a random effect model, yielded an overall OR of 3.49 (95% CI, 1.24, 9.83), with $I^2 = 92.36\%$ (pronounced heterogeneity) and $P = 0.018$ (Fig. 2).

Subgroup analysis results (by study design)

We stratified the meta-analysis by study design: case-control studies: OR 1.85 (95% CI, 0.96, 3.59), $I^2 = 75.92\%$, $P = 0.065$; and cohort studies (cases with silicosis): OR 9.71 (95% CI, 1.13, 83.58), $I^2 = 72.65\%$, $P = 0.038$ (Fig. 2).

Risk of bias across the studies (funnel plot)

We used the funnel plot, Egger's test and Higgins index to detect possible biases among the studies (Fig. 3). Using the Higgins I^2 index, heterogeneity can be classified as high ($I^2 = 92.36\%$). The visible asymmetry in the funnel plot confirms the presence of heterogeneity between the studies (two rates fall outside the funnel). The remaining four studies are located visually in the upper area of the plot and inside the funnel. The P -value of Egger's regression test is significant ($P < 0.05$) for publication bias.

Discussion

Summary of evidence

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the relationship between SLE onset and previous occupational exposure to FCS.

Despite FCS having long been considered a possible risk factor for SLE, only a few studies have been conducted in the past and none in the past decade, and hence this association remains somewhat unclear. Indeed, recent studies conducted on workers or community residents in the area of the terrorist attack on the twin towers of 11 September 2001 have shown that exposure to the intense dust cloud, whose major component was crystalline silica, significantly increased the risk of a new onset of systemic autoimmune diseases [31, 32]. Among these, the most frequent is represented by

RA followed by Sjögren's syndrome and SLE [31]. Exposure to environmental toxicants is also a known cause of development of a condition called auto-immune/inflammatory syndrome induced by adjuvants (ASIA) in which some cases of SLE could also be classified [33, 34].

Over the years, the occupational exposure levels of FCS have been tightly regulated and progressively reduced by agencies and national laws. The ACGIH Threshold Limit Value-Time Weighted Average (TLV-TWA) value has dropped from 0.1 mg/m³ (up to 2000) to 0.05 mg/m³ and subsequently, since 2007, to 0.025 mg/m³ [35]. In the USA, the Occupational Safety and Health Administration's permissible exposure limit has been 50 µg/m³ from 2016, whereas the recent EU directive 2017/2398 on carcinogenic substances in the workplace has established an exposure limit value (0.1 mg/m³) [36].

In the literature there are several case reports, not useful for the purposes of our analysis. Experimental evidence on the association between FCS and SLE relies on experimental studies on mixed mice susceptible to SLE, showing that FCS accelerates the development of SLE [37, 38].

Our systematic research of all the available evidence led us to include four case-control studies and two cohort studies in the analysis. Rosenman *et al.* [29] (Table 1) was included in the systematic review but not in the meta-analysis as the population studied was partially overlapping with that of Makol *et al.* [22], which analysed cases (from the Michigan Silicosis Surveillance records) for a longer time period (from 1985 to 2006).

All the studies were conducted in North America with the exception of one study [30] conducted on North European (Swedish and Danish) subjects. We can speculate that most of the studies have been conducted in North America due to scrupulous policies and surveillance systems for silicosis and to the fact that incidence of SLE and workers exposed to silica are higher compared with Europe [39, 40].

The demographic characteristics of the cases are quite heterogeneous; in two studies [21, 26] there is a prevalence of white subjects (respectively 82% and 72%) while two other studies [27, 28] show the opposite situation in favour of African-Americans (respectively 84% and 60%). In the remaining three studies [22, 29, 30] no information is provided about ethnic groups. It is important to remember that SLE is two to three times more prevalent among women of colour [41].

The results of our meta-analysis partially support the association between occupational exposure to FCS and SLE. The final magnitude of the association obtained from the meta-analysis is statistically significant [OR 3.49 (95% CI, 1.24, 9.83)], although we found an important heterogeneity between the studies that can be explained by the different study designs, populations and exposure assessments. In order to reduce the heterogeneity, we performed a further sub-meta-analysis excluding the studies on silicosis patients. In this case,

the overall OR was reduced to 1.85 (95% CI, 0.96, 3.59), statistically not significant. From our point of view, such results show the importance of considering the studies carried out on patients with silicosis. This is a progressive and irreversible disease caused by inhaling large amounts of FCS, usually over decades (10–20 years) [42]. In rare cases, following massive exposure it can occur in a few months [42]. Studies investigating people with silicosis overcome any uncertainty about occupational exposure to FCS; in the other studies, which represent the majority, the assessment of exposure to FCS is prone to a profound bias as it was investigated on the basis of personal questionnaires, or drawn from medical records. In studies investigating the role of occupational–environmental risk factors, the importance of exposure assessment is pivotal [43].

Results of our study require caution, deriving from main limitations of included studies. Many studies were heterogeneous, and the sample sizes were very different: in the case–control studies there were 40 [26], 529 [21], 95 [27] and 13 [11], and in the cohort studies 1 [22] and 8 [30] (these data refer only to the outcome FCS–SLE) (Table 1).

Cohort studies in particular registered small samples size. Nonetheless, we decided to not exclude any study from the meta-analysis based on sample size, as long as it fulfilled our *a priori* inclusion criteria. In fact, it is also known that in a meta-analysis, smaller studies together with the others have the power to detect the intervention effect that they would not be able to do individually.

We are aware, anyway, that larger samples size might yield more precise estimates than smaller samples [44] and these latter could also tend to report greater intervention effects [45]. In this regard, we paid attention to possible biases by investigating not only the study size but also the study quality through the use of the NOS.

The heterogeneity between the studies may rely on the different study design: the case–control study based on death certificates lacks information on the diagnosis of SLE, and the outcome is slightly different compared with the rest of the studies. In Brown *et al.* [30] several pieces of methodological information are missing. Another main limitation is that of exposure assessment. Data were obtained from face-to-face and telephone interviews and from death certificates (Table 1). While personal interviews might be subjected to recall bias, mortality studies using occupational job coding (ICD) might be prone to errors and misclassifications.

One study [26] in particular did not specify the duties of workers exposed to FCS. In another case, the data relating to the jobs were incomplete [28]. This general lack of precise and detailed information on the type of duties covered prevented us from performing further analyses on specific job tasks or gender.

The risk of heterogeneity between cases is quite relevant and common in meta-analyses and we cannot rule

out being exempt. Exposure to high levels of FCS is characteristic of the so-called ‘dusty trades’ and foundry works, which are also the main areas of employment of workers included in our study. We hope that in the future more studies will be available, thus allowing sample size to be adequate to investigate subgroups of work tasks. The heterogeneity of tasks between the studies can be considered one of the main reasons that led us to choose a random-effect model.

Exposure to confounding risk factors like pesticides [28] in farmers exposed to FCS could have modified the outcome (confounding bias). Anyway, we are aware that such bias is almost unavoidable.

Limitations

Outcome level—meta-analysis

A main limitation of meta-analysis is that the investigated populations, the FCS exposure assessment and the outcome definitions are not the same across the studies.

Study and review level

As evidenced by the use of the NOS, the quality of the studies is comparable and attested to acceptable values for the case–control studies (Table 2). A poor result was attributed to two studies in particular [21, 30]. Publication bias is shown by asymmetry of the funnel plot.

Conclusions

To the best of our knowledge the present study represents the first systematic review and meta-analysis on the correlation between occupational exposure to FCS and SLE.

The result of our main meta-analysis shows that FCS exposure may increase the risk of SLE, in particular when considering patients with silicosis. We can therefore speculate that when occupational exposure to FCS is reliable, the correlation with SLE is stronger. We registered a lack of cohort studies, probably due to the fact that it would be complicated to carry them out since SLE is a relatively rare disease in the population. We hope that new case-report and cohort studies will be conducted in the near future. Dose–response analyses might well reveal important information, but such studies require accurate exposure assessment. Further studies on this topic are necessary to draw more consistent evidence. In the meantime, occupational physicians and rheumatologists should be aware of this correlation and consider a work-related aetiology in certain SLE workers.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit

sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008;358:929–39.
- Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110–21.
- Koeger AC, Lang T, Alcaix D *et al.* Silica-associated connective tissue disease. A study of 24 cases. *Medicine (Baltimore)* 1995;74:221–37.
- Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
- Petri M, Orbai AM, Alarcón GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- Aringer M, Costenbader K, Daikh D *et al.* European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:1400–12.
- Lawrence RC, Helmick CG, Arnett FC *et al.* Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778–99.
- Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum* 2007;56:2092–4.
- Maningding E, Dall'Era M, Trupin L, Murphy LB, Yazdany J. Racial/ethnic differences in prevalence of and time to onset of SLE manifestations: the California Lupus Surveillance Project (CLSP). *Arthritis Care Res* 2020;72:622–9.
- Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. *Rheumatology (Oxford)* 2017;56:i67–77.
- Parks CG, de Souza Espindola Santos A, Barbhayia M, Costenbader KH. Understanding the role of environmental factors in the development of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2017;31:306–20.
- Parks C, De Roos A. Pesticides, chemical and industrial exposures in relation to systemic lupus erythematosus. *Lupus* 2014;23:527–36.
- Wu P, Hyodoh F, Hatayama T *et al.* Induction of CD69 antigen expression in peripheral blood mononuclear cells on exposure to silica, but not by asbestos/chrysotile-A. *Immunol Lett* 2005;98:145–52.
- Hayashi H, Miura Y, Maeda M *et al.* Reductive alteration of the regulatory function of the CD4+CD25+ T cell fraction in silicosis patients. *Int J Immunopathol Pharmacol* 2010;23:1099–109.
- Wu P, Miura Y, Hyodoh F *et al.* Reduced function of CD4 + 25+ regulatory T cell fraction in silicosis patients. *Int J Immunopathol Pharmacol* 2006;19:357–68.
- Suni L, Hiroaki, H, Hidenori, M *et al.* Silica-induced immunotoxicity: Chronic and aberrant activation of immune cells. In: T Otsuki, C Petrarca, M Di Gioacchino, eds. *Allergy and Immunotoxicology in Occupational Health. Current Topics in Environmental Health and Preventive Medicine.* Singapore: Springer, 2017:15–26.
- Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- Mattioli S, Zanardi F, Baldasseroni A *et al.* Search strings for the study of putative occupational determinants of disease. *Occup Environ Med* 2010;67:436–43.
- UTHealth, The University of Texas. Search Filters for Various Databases: PubMed. http://libguides.sph.uth.tmc.edu/search_filters/pubmed_filters (29 December 2019, date last accessed).
- PRISMA. PRISMA Flow Diagram. <http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx> (25 November 2019, date last accessed).
- Gold LS, Ward MH, Dosemeci M, De Roos AJ. Systemic autoimmune disease mortality and occupational exposures. *Arthritis Rheum* 2007;56:3189–201.
- Wells GA, Shea B, O'Connell D *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf (29 December 2019, date last accessed).
- Biostat. Comprehensive Meta-Analysis. https://www.meta-analysis.com/pages/why_do.php?cart=BM2Y3556215 (29 December 2019, date last accessed).
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- Cooper GS, Wither J, Bernatsky S *et al.* Occupational and environmental exposures and risk of systemic lupus erythematosus: silica, sunlight, solvents. *Rheumatology* 2010;49:2172–80.
- Finckh A, Cooper GS, Chibnik LB *et al.* Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. *Arthritis Rheum* 2006;54:3648–54.
- Parks CG, Cooper GS, Nylander-French LA *et al.* Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. *Arthritis Rheum* 2002;46:1840–50.
- Makol A, Reilly MJ, Rosenman KD. Prevalence of connective tissue disease in silicosis (1985–2006)—a report from the state of Michigan surveillance system for silicosis. *Am J Ind Med* 2011;54:255–62.

- 29 Rosenman KD, Moore-Fuller M, Reilly MJ. Connective tissue disease and silicosis. *Am J Ind Med* 1999;35: 375–81.
- 30 Brown L, Gridley G, Olsen J *et al.* Cancer risk and mortality patterns among silicotic men in Sweden and Denmark. *J Occup Environ Med* 1997;39:633–8.
- 31 Webber MP, Moir W, Zeig-Owens R *et al.* Nested case-control study of selected systemic autoimmune diseases in World Trade Center rescue/recovery workers. *Arthritis Rheumatol* 2015;67:1369–76.
- 32 Miller-Archie SA, Izmirly PM, Berman JR *et al.* Systemic autoimmune disease among adults exposed to the September 11, 2001 terrorist attack. *Arthritis Rheumatol* 2020;72:849–59.
- 33 Watad A, Quaresma M, Bragazzi NL *et al.* The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. *Clin Rheumatol* 2018;37:483–93.
- 34 Scanzi F, Andreoli L, Martinelli M *et al.* Are the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and the undifferentiated connective tissue disease (UCTD) related to each other? A case-control study of environmental exposures. *Immunol Res* 2017;65:150–6.
- 35 American Conference of Governmental Industrial Hygienists (ACGIH). Silica, Crystalline: alpha-Quartz and Cristobalite: TLV(R) Chemical Substances, 7th Edition Documentation. Cincinnati, OH: ACGIH, 2010.
- 36 Occupational Safety and Health Administration (OSHA). Small Entity Compliance Guide for the Respirable Crystalline Silica Standard for Construction. Washington, DC: OSHA, 2017.
- 37 Brown JM, Archer AJ, Pfau JC, Holian A. Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice. *Clin Exp Immunol* 2003; 131:415–21.
- 38 Bates MA, Brandenberger C, Langohr II *et al.* Silica-triggered autoimmunity in lupus-prone mice blocked by docosahexaenoic acid consumption [published correction appears in *PLoS One* 2017;12:e0171877] [published correction appears in *PLoS One* 2019;14:e0220469]. *PLoS One*. 2016;11:e0160622.
- 39 Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology* 2017;56:1945–61.
- 40 Balaan MR, Banks DE. Silicosis. Occupational and environmental medicine, 3rd edn. Philadelphia: Lippincott-Raven, 2008: 435–48.
- 41 Wallace DJ, Hahn BH. Dubois' lupus erythematosus and related syndromes. Philadelphia, USA: Elsevier Saunders, 2013.
- 42 National Health Service. Silicosis. <https://www.nhs.uk/conditions/silicosis/> (29 December 2019, date last accessed).
- 43 Ge CB, Friesen MC, Kromhout H *et al.* Reliability of exposure assessment methods in occupational case-control studies in the general population: past, present, and future. *Ann Work Expo Health* 2018;62:1047–63.
- 44 Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-Analysis. Hoboken, NJ: Wiley, 2009.
- 45 Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS One* 2013;8:e59202.