Review

An update on occupational exposures in systemic sclerosis: a narrative review on risk factors and characteristic disease phenotypes in silica- and organic solvent-exposed patients

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ABSTRACT

Occupational exposures, particularly silica and organic solvents, have been implicated in the aetiopathogenesis of systemic sclerosis (SSc). Epidemiological studies suggest that these exposures may trigger immune activation with subsequent development of inflammation, fibrosis and clinically relevant disease. However, the relationship between specific exposures and distinct SSc phenotypes remains poorly defined due to recall bias, exposure misclassification and reliance on self-reported data. This narrative review summarises, in particular, the current literature on silica and organic solvent exposure and its prevalence in various global SSc cohorts with the aim to identify potential demographic and clinical risk factors. Despite the lack of standardised reporting of quantitative exposure information, most studies show an association between silica and organic solvent exposure and severe SSc disease phenotypes. Major organ involvement including cardiac involvement, severe interstitial lung disease (ILD), renal crises and severe gastrointestinal involvement by Medsger severity score have been linked to cumulative exposure scores with potentially higher mortality rates and poorer prognosis in this subset of patients. The finding of a strong association between male gender and silica or solvent exposure in a predominantly female-driven disease represents an important risk factor that should prompt the attending clinician to find a possible exposure link.

Introduction

Since 1914, when Scottish physician Bramwell (1) made an astute observation of silica exposure in nine stonemasons with "sclerodermia", multiple scientific studies have been conducted trying to determine a causal link between connective tissue diseases (CTD) and various occupational and environmental exposures. Indeed, autoimmune rheumatic diseases (AIRDs) including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Sjögren's syndrome, with their unknown multifactorial aetiology and links to both genetic and environmental factors, have created an attractive avenue of research into the pathophysiological development of these orphan diseases.

While contemporary estimates of the overall incidence of autoimmune diseases are scarce, the National Health and Nutrition Examination Survey (NHANES) data in the US (1988-2012) has shown increasing incidence and a prevalence globally ranging from 3.7% to 7.1% a year as well as an increase in positive ANA prevalence of 5.1%, especially in adolescents (2). Similarly, an increasing trend was noted in a recent UK-based population study with incidence rate ratios (95% CI) ranging from 1.15 (1.0 - 1.28) to 2.09 (1.84 – 2.37) (3). This rising trend, together with continually evolving disease presentations into different phenotypes and endotypes as well as varying socioeconomic, seasonal and regional disparities within the different AIRDs is highly suggestive of environmental influence playing a key role in disease pathogenesis and severity (3).

Among these environmental factors, occupational exposures represent a large

Table I. Frequencies of environmental exposures in systemic sclerosis populations.

Population/ Year	Total cohort size	Exposure determination	Exposure type	Number exposed (%)	Reference
France (2014)	100	Questionnaire; Experts: occupational medicine and epidemiologists	Silica Organic solvents	18 (18) 33 (33)	21
Brazil (2016)	947	Questionnaire	Silica	9 (0.9)	25
Belgium (2018)	103	Questionnaire; Occupational medicine expert	Silica Organic solvents	55 (57.3) 11 (11.5)	11
Italy (2018)	80	Questionnaire. Environmental Scanning Electron Microscopy (ESEM): morphological characterisation; Energy-dispersive X-ray Spectroscopy (EDS): chemical identification of particles	Silica	43 (54)	27
Australia (2020)	1670	Questionnaire	Silica	126 (7.5)	18
Brazil (2021)	662	Questionnaire	Organic solvents Silica	36 (51.4) 14 (20)	9
Denmark (2021)	252	Questionnaire. Semi-quantitative exposure assessment: SYNGEM job exposure matrix	Silica	Cumulative exposure per 50 mg/m^3-years: IRR 1.10 (1.03–1.18)	16
Canada, Mexico (2022)	1439	Questionnaire	Silica	95 (6.6)	17
France (2022)	210	Questionnaire; Experts: occupational medicine; Semi-quantitative exposure assessment: Matgéné job-exposure matrix	Silica Organic solvents	30 (14.3) 53 (25.2)	31
Spain (2024)	255	Interview	Silica Organic solvents	91 (35.8) 12 (4.9)	10
China (2024)	310	Silicosis by XRays	Silica	72 (23.2)	28
Canada (2024)	1439	Questionnaire	Organic solvents	290 (20.2)	33

risk category which involves heightened and long-term exposure to potentially harmful agents that may eventually contribute to chronic inflammation and autoimmunity. To date, the commonly mentioned occupational agents discussed in epidemiological and experimental studies of CTDs consist of silica dust (quartz), solvents, pesticides and plastics and most of these studies are clustered around SSc and scleroderma-like diseases. Despite these associations, the impact of occupational exposures and clinical trajectory of AIRDs remains underexplored. The aim of this narrative review is to examine the currently published literature on commonly mentioned occupational exposures in SSc, in order to identify potential risk factors and to explore how these exposures may contribute to specific SSc disease phenotypes.

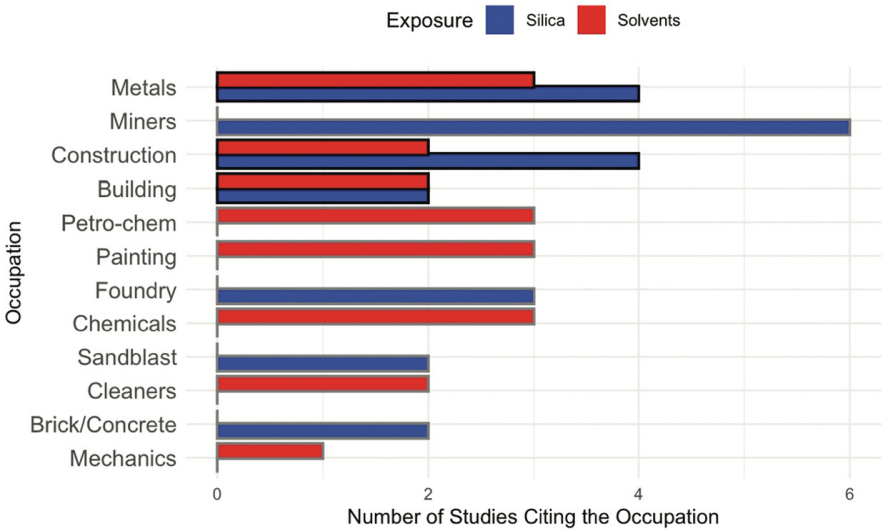

Fig. 1. High risk occupations for silica and solvent exposure in systemic sclerosis.
Sandblast: sandblasters; Petro-chem: petro-chemical industry; Painting: paint industry; Miners: mining industry; Metals: metal industry; Mechanics: auto-mechanic industry; Foundry: foundry workers; Construction: construction workers; Cleaners: cleaning industry; Chemicals: chemical industry; Building: building workers; Brick/concrete: brick and concrete workers.

Methods

A narrative literature search was performed in November 2024 across the PubMed database to address the research question of occupational exposures in SSc: its cumulative prevalence, notable common exposures and associations to specific SSc organ involvement. The database was searched with a keyword search using terms related to SSc and environmental factors, oc-

cupational exposures and clinical and epidemiological risk factors. After noting most studies linked to occupational silica and organic solvent exposure, search results were refined and limited using MeSH major topic or keyword title search (silica AND SSc AND occupational exposure; organic solvents AND SSc AND occupational exposure) to identify epidemiological studies discussing these two specific exposures with SSc and subsequent organ involvement. All articles published within the past ten years were reviewed. In addition, select abstracts from the American Congress of Rheumatology (ACR) Convergence 2024, including those presenting emerging research directly relevant to this topic, were examined. A formal review of all recent international rheumatology conference abstracts was not performed. Several manuscripts published prior to 2014 were also referenced as key studies to highlight historical context to the current literature. Only studies published in English were considered for inclusion.

Results

Occupational exposure in systemic sclerosis

Systemic sclerosis is a rare autoimmune disease, predominantly affecting females, and is characterized by a triad of autoantibody formation, vasculopathy and fibrosis of the skin and internal organs (4, 5) . In a recent global meta-analysis, the overall pooled prevalence of SSc was 17.6 (95% CI 15.1, 20.5) per 100 000 and the overall pooled incidence rate of SSc was 1.4 (95% CI 1.1, 1.9) per 100 000 person-years, with significant regional variations observed in these reported estimates (6). The aetiopathogenesis is complex with genetic studies on monozygotic twins showing a low concordance in the clinical onset of SSc thus highlighting the role of environmental factor influence on a genetically susceptible individual leading to the initiation of clinically relevant disease (7, 8). Potential mechanisms postulated include loss of self-tolerance causing an autoinflammatory state, direct activation of the immune system and molecular mimicry(9). Epidemiological studies have identified several occupational factors suspected of contributing to SSc development (10) . The frequency of exposure, identified by interviews of occupational history and structured questionnaires, ranges between 10.6-72.9 % in retrospective cohorts (11-13). These include silica minerals, chlorinated and aromatic hydrocarbon solvents, vinyl chloride and epoxy resin plastics, pesticides and hand-transmitted vibrating tools (14).

Silica: risk factors and characteristic organ involvement

Silica (or silicon dioxide) is found in about 92% of all rocks and has 3 main crystalline structures: quartz, tridymite, and cristobalite (15). Since 1957, after noting an increased incidence of SSc (7.7 cases per 100,000 miners per year) in silica-exposed South African gold miners (16), multiple nation-wide studies from the United States, Europe, Australia and Canada have reinforced this causal link reporting higher prevalence of silica exposure in SSc patients in comparison to the general population (17-21) (Table I). The combined estimator of relative risk (CERR) of occupational silica exposure for scleroderma has been shown to be around 3.20 (95% CI 1.89, 5.43) (22), and a significant risk odds ratio (OR) of 5.32 (p=0.0001) was seen especially in males and associated mainly with cumulative exposure. These gender differences may reflect underlying disparities in employment sectors or job roles, which influence the likelihood and intensity of occupational exposure (23). Recently this overall risk was also shown to increase further with increasing cumulative exposure after entering the workforce [IRR: 1.07 (1.05–1.09) per 50 mg/m^3-years] in a Danish working population (18).

Commonly mentioned occupations associated with silica exposure and SSc development include miners, metal and construction workers, foundry workers, quarryman, sandblasters and sandstone sculptors (Fig. 1). Among males with SSc, construction workers showed a 4- to 10-fold higher risk compared to the general working population (24, 25). The average duration of silica exposure was 13.7 years (25), with the onset of SSc occurring approximately 24 years after the initial exposure (13). In some cases, silica exposure continued up to the time of SSc onset. The mean age at SSc onset, as defined to the onset of the first non-Raynaud symptom, was between 47-50.4 years (26-29); however, a younger median age at onset (p=0.042) was recently identified (between 35-50 years) in an ambispective study performed in 3 tertiary Spanish hospitals (30). There is a strong association noted with male sex, silica exposure and the development of SSc with an OR ranging between 3.06-9.63 (23, 31).

Occupational exposure to silica may also be associated with specific organ involvement and poor outcomes (Table II). Clinical data from 254 silica-exposed SSc patients demonstrated associations with diffuse cutaneous SSc (DcSSc) and interstitial lung disease (ILD) (12). Similar findings were echoed in various other SSc cohorts involving more severe diffuse forms, anti-Scl-70 positivity and with lower survival rates (23, 26). In Belgium, a trend towards more severe SSc disease phenotypes with higher disease activity scores were noted (mean DAS 2.5 versus 1.5, p=0.055), but did not reach statistical significance (13) (Fig. 2).

Recently, in a multicentre retrospective French cohort of 210 SSc patients, occupational exposures were standardised quantitatively to yield a cumulative exposure score (CES). Occupational exposure was found in 37.6% of the cohort with the most frequent exposures being chlorinated solvents (25.2% of patients), crystalline silica (14.3% of patients), and epoxy resins (11.0% of patients). Silica exposure was mostly seen in professions linked to the building trade, foundry, and pottery or porcelain factories. SSc-ILD was diagnosed in 43.8%, and while a comparable frequency over the course of follow-up between genders was noted, the available data did not permit robust gender-stratified analysis, as highlighted by the authors. In their follow-up analysis using forced vital capacity (FVC) measurements collected over a mean of 2-years and with at least 2 FVC measurements recorded,

Table II. Systemic sclerosis phenotypes associated with silica and solvent exposure.

Clinical Feature	Silica OR (95% CI)	Solvents OR (95% CI)
Males	0.15 – 19.31 (0.06 – 69.86)	4.01 (1.23 – 13.37)
DcSSc Subtype	1.95 – 4.13 (1.28 – 13.74)	1.10 – 3.81 (0.82 – 8.95)
Anti-Scl 70 Positivity	2.18 – 3.71 (0.51 – 11.43)	1.27 – 2.67 (0.85 – 6.89)
Myopathy	3.09 (1.67 – 5.73)	
Joint Contractures	1.8 (1.0 – 3.3)	
ILD	8.06 (1.00 – 31.79)	2.64 (1.16 – 5.98)
Severe ILD*	2.08 (1.00 – 4.27)	
Severe GI disease**	1.11 – 2.43 (1.01 – 3.71)	2.43 (1.60 – 3.71)
SRC	2.13 (1.15 – 3.93)	2.13 (1.15 – 3.93)
Cardiac SSc	HR= 4.225 (1.090 – 16.383)	
Digital ulcers	2.82 (0.87 – 10.02)	2.74 (1.24 – 6.11)
Cancer	5.97 (1.55 – 23.01)	6.16 (1.69 – 27.55)
Increased mortality	HR 1.45 (0.96 – 2.19)	

OR: odds ratio; CI: confidence interval; DcSSc: diffuse cutaneous systemic sclerosis; Anti-Scl 70: antibody to Scl-70; ILD: interstitial lung disease; GI: gastrointestinal; SRC: scleroderma renal crisis; SSc: systemic sclerosis; HR: hazards ratio

Data in this table represent an aggregation of findings from multiple published cohorts, as cited throughout the manuscript reference list.

*Severe ILD as defined by the presence of ILD on HRCT and FVC<70% (17).

**Severe GI disease as defined by higher GI-14 and Medsger GI scores (17).

they demonstrated a moderate inverse correlation between FVC decline and exposure to crystalline silica (r=-0.51). This study also showed an independent association with decline in FVC over time and with occurrence of FVC decline of ≥10% from baseline (p<0.05), independent of sex (32).

Huo *et al*. (29) showed increased frequency of ILD, lower partial pressure of oxygen (pO_2), arthritis/arthralgia and cardiac involvement in 72 Chinese SSc patients with silica exposure. In their multivariate analysis, silica was shown to be an independent risk factor for death and survival analysis showed a decreased survival rate in this exposed group of SSc patients. Notably there was an increased incidence of cardiac-related deaths. Prior studies have also noted cardiac involvement in silica-exposed SSc individuals which include diastolic dysfunction (13), lower median values of left ventricular ejection fraction (23), myocardial involvement and tricuspid regurgitation (29). Digital ulcers (23, 33), oesophageal involvement (26), myositis (11, 28) and pigmentary disorders (11) were also demonstrated in various cohorts (Table II).

Organic solvents: risk factors and characteristic organ involvement

Organic solvents are a frequently identified occupational chemical exposure and are carbon-containing liquids which include benzene and toluene (aromatic solvents) and vinyl chloride and trichloroethylene (chlorinated solvents) (34). These chemicals are used in dry cleaning agents, paint thinners, nail polish, glues and degreasers, and are encountered in many occupations like paint and coating industries, chemical/plastic/rubber manufacturing, construction workers (painters, decorators and woodworkers), dry cleaners, automotive industry and laboratory technicians (34, 35).

Since the first case in 1957 describing a woman with DcSSc in Germany who was exposed for years to trichloroethylene (36), multiple case reports, case series and epidemiological studies have attempted to investigate the role of organic solvents in the development of SSc (Table I). Common high-risk occupations for solvent exposure in SSc include painters, chemical and petrol-chemical industry, metal and construction workers and cleaning industry (Fig. 1). In a 2012 metanalysis analysing eight studies on SSc, exposure to organic solvents was shown to be statistically related to SSc development with an OR of 2.54 (95% CI: 1.23, 5.14; p=0.011) (37). The risk of SSc among men exposed to solvents has been found to be higher than among women, with an OR ranging from 2.40 (95% CI 1.44–4.01) to 5.28 (95% CI 3.48, 8.05) for men (31, 38).

Organic solvents have demonstrated significant links to specific clinical phenotypes in SSc (Table II). In the French case-control study, Marie *et al*. (33) used a standardised questionnaire and a blinded expert committee to determine occupational history exposure to organic solvents in 142 SSc patients. In 50 patients confirmed with exposure, these patients had more diffuse cutaneous disease and anti-Scl 70 antibody positivity, with poorer prognosis suggesting that exposure to these chemicals may be predictive for severe SSc. Interestingly, ILD was noted to be the most frequent first non-Raynaud's manifestation in these solvent-exposed SSc patients, and those exposed to chlorinated solvents developed more severe ILD with more ground-glass opacities on HRCT (p=0.03) and lower median FVC (p=0.03) and DLCO values (p=0.009). Microangiopathy with digital ulcers and lower median value of LVEF, as well as higher rates of cancer were also noted to be significant in the exposed group. A higher median modified Rodnan skin score (mRSS) was observed in patients exposed to chlorinated solvents (mRSS = 8) compared to those exposed to aromatic solvents and white spirits (mRSS = 4; p=0.002) (Fig. 3).

In Spain 259 SSc patients were identified with occupational solvent exposure through an intensive questionnaire and blood samples which quantified 61 micro-, macro- and toxic elements (30). Using the Canadian Job Exposure Matrix (CANJEM), they identified the relationship between work activities and pollutant exposure. CANJEM (39) represents a large database, from Montreal Canada, of retrospective exposure information covering many occupations and agents, that can be used to support exposure assessment efforts in epidemiological and occupational studies. It provides estimates of the probability of exposure among those in a given occupation, and in those who are exposed, it can provide various metrics of exposure. In this Spanish cohort, exposure to organic solvents increased the presence of diabetes (OR 2.3; [95%

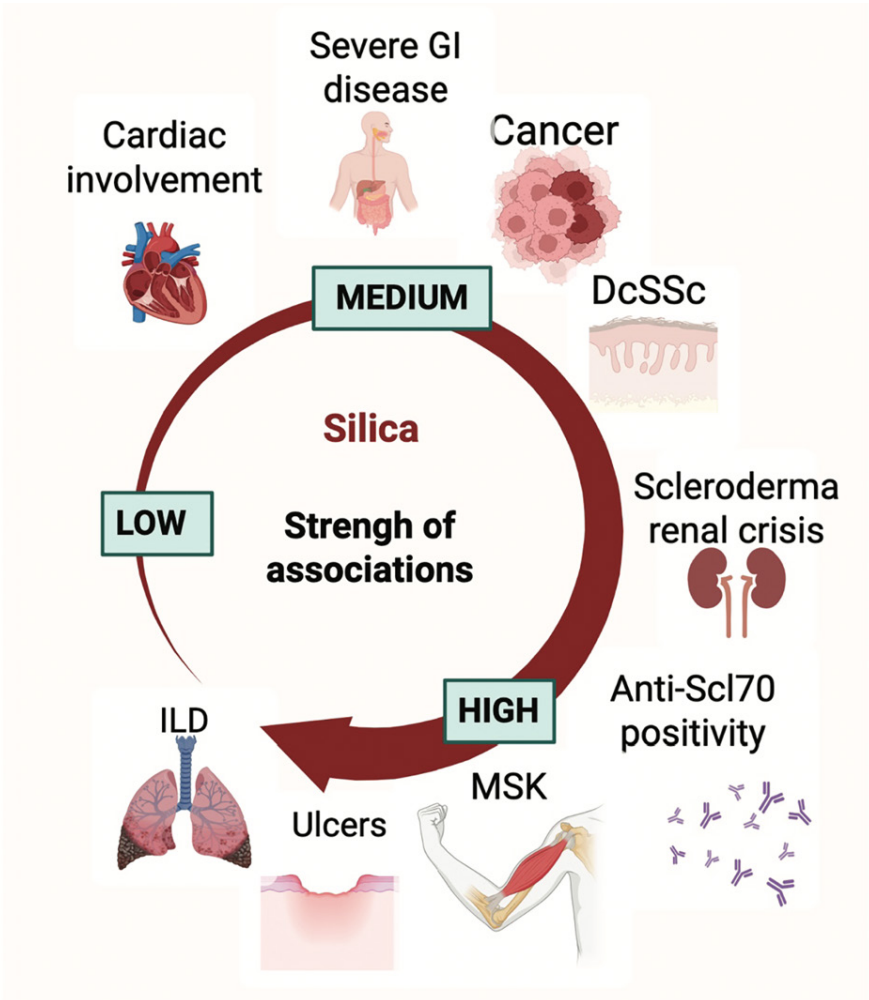

Fig. 2. Strength of association between silica exposure and clinical features in systemic sclerosis.
The figure shows the clinical features of SSc and their respective strengths of association with exposure to silica.
ILD: interstitial lung disease; GI: gastrointestinal; SSc: systemic sclerosis; MSK: musculoskeletal; Scl70: anti-topoisomerase I antibodies; dcSSc: diffuse cutaneous systemic sclerosis.
The figure was created with www.biorender.com (agreement no. VW28BG9M3R).

CI: 1.0, 5.3], *p*=0.050), autoimmune hepatitis (AIH) (OR 8.17; [95% CI: 1.0, 377.8], *p*=0.02) and almost the odds of cutaneous involvement (OR 3; [95% CI 1.0, 13.6], *p*=0.056).

Recently, in Canada 20.2% of 1439 SSc patients in the Canadian Scleroderma Research Group were identified as being exposed to organic solvents using self-reported measures. When comparing the exposed to the non-exposed group, the former showed a non-statistically significant trend toward diffuse SSc, higher anti-topoisomerase and lower anti-centromere antibody positivity. After adjusting for confounders on multivariate analysis solvent-exposed SSc patients showed characteristics of more severe disease with a higher risk of renal crisis (SRC) (OR 2.13; [95% CI: 1.15-3.93], *p*=0.050) and severe gastrointestinal disease by Medsger severity score (*p*=0.019). There was a trend toward an increasing mortality rate in the exposed group (34).

Multiple occupational exposures have been postulated to play a role in the development of SSc, with the strongest epidemiologic support surrounding silica and solvent exposures. The reported frequencies of exposures in the different cohorts varies widely (Table I). This could likely be because epidemiological study designs in this area mainly encompass cohort studies, case-control studies and case reports, with each displaying its own set of limitations. As seen in most of these studies discussed, methods for quantifying occupational exposure were determined mainly by self-reporting interviews and structured questionnaires, which introduces recall bias and thereby limiting the accuracy of past exposures with either under- or overestimation. Subsequently, this self-reported method can also lead to misclassification bias when categorising exposures based primarily on participant responses.

In the study by Marie *et al*. (23, 33) who determined that overall, 42.3% of their French SSc cohort had occupational exposure to both silica and organic solvents, the use of the questionnaire together with a blinded expert committee of occupational physicians and epidemiologists certainly lends more reliability to the exposure information. This allows for semi-quantitative or probabilistic exposure estimates and a blinded panel review prevents confirmation bias in this SSc cohort. This combination method could be used to reduce bias, improve classification accuracy and strengthen causal inference. The use of job exposure matrices (JEMs) in studies presented by Denmark (18), France (32) and Spain (30), also enhances the credibility and robustness of exposure assessment as they estimate exposure levels to specific occupations, job titles and industries. Ferri *et al*. (28) demonstrated silica exposure in 54% of their Italian SSc cohort using firstly a questionnaire to identify the exposed patients and then morphologically and chemically identifying these nano-particles using electron microscopy and spectroscopy, respectively. This further strengthens causal inference by directly linking silica to the studied SSc population and also provides quantitative exposure data thus making it possible to assess dose-response relationships.

Discussion

Multiple occupational exposures have been postulated to play a role in the development of SSc, with the strongest epidemiologic support surrounding silica and solvent exposures. The reported frequencies of exposures in the different cohorts varies widely (Table

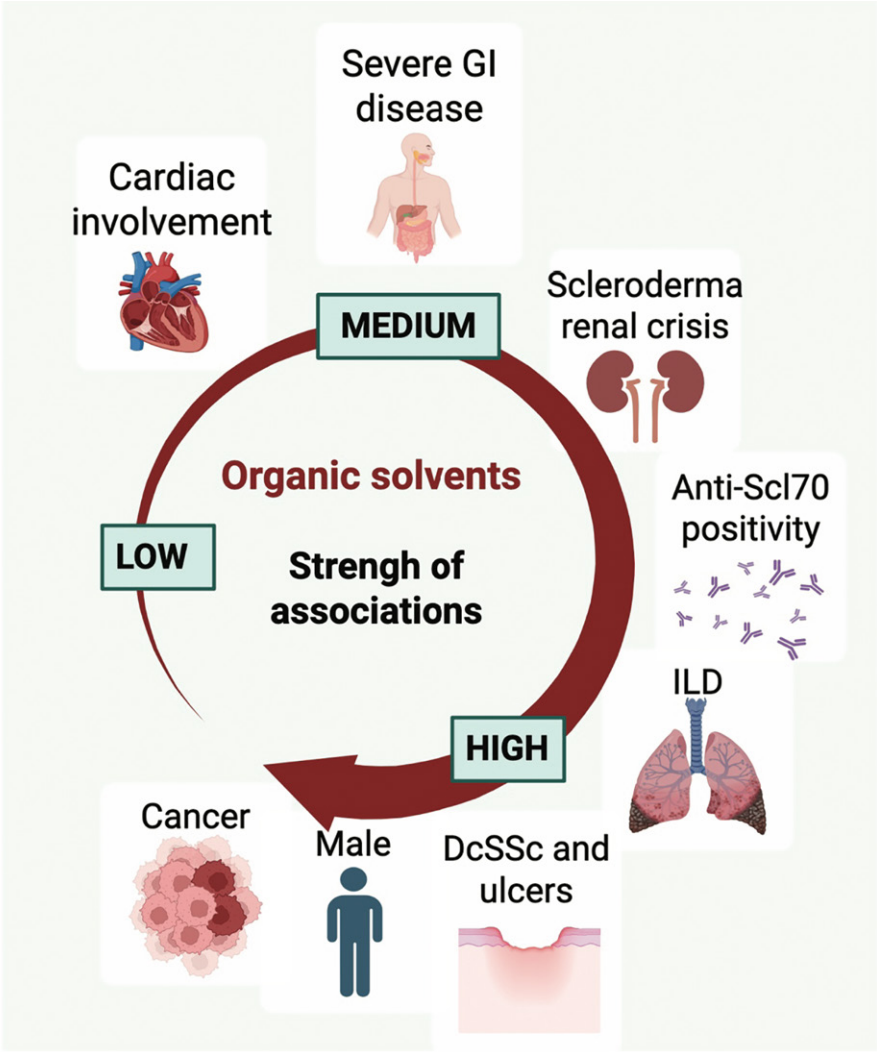

Fig. 3. Strength of association between organic solvents exposure and clinical features in systemic sclerosis.
The figure shows the clinical features of SSc and their respective strengths of association with exposure to organic solvents.
ILD: interstitial lung disease; GI: gastrointestinal; Scl70: anti-topoisomerase I antibodies; dcSSc: diffuse cutaneous systemic sclerosis.
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I). This could likely be because epidemiological study designs in this area mainly encompass cohort studies, case-control studies and case reports, with each displaying its own set of limitations. As seen in most of these studies discussed, methods for quantifying occupational exposure were determined mainly by self-reporting interviews and structured questionnaires, which introduces recall bias and thereby limiting the accuracy of past exposures with either under- or overestimation. Subsequently, this self-reported method can also lead to misclassification bias when categorising exposures based primarily on participant responses.

The true determination of significant exposure from organic solvents is also debatable and yet to be elucidated. Importantly, there are difficulties when trying to identify chemical compositions of various solvent agents, isolating the pathological substrate involved and then further quantifying the intensity, frequency and duration of exposure. Exposure biomarkers could potentially bridge this gap to assess these individual exposures, but the currently available urinary biomarkers for solvents are meant to be measured during exposure or within 24 hours of the end of the exposure to get a meaningful result (40). More work needs to be done to formulate biomarkers that could be used to determine causality links in CTDs where there are delayed temporal associations to the exposure variable. This in itself presents a potential avenue for further research.

Irrespective of the heterogenous study designs and the varying exposure method determination, the majority show a link to specific SSc clinical phenotypes (Supplementary Fig. S1). Both silica and organic solvents are strongly associated with male sex, DcSSc and anti-Scl 70 positivity. ILD was noted to be prominent feature in both exposures while silica was associated with a 2-fold risk for severe ILD (defined as the presence of ILD and FVC<70%) after adjusting for age, sex, diffuse disease, immunosuppressive medication, disease duration, ethnicity and smoking (19). Severe GI disease, SRC and digital ulceration was seen with varying degrees in both exposure groups. In the silica-exposed group, musculoskeletal involvement with myopathy and tendon friction rubs were evident, while in the solvent-exposed group, there was a stronger association with cancer. The deep pathophysiological mechanisms related to occupational chemical exposure and how to integrate them in the complex progression of SSc still to be better investigated (34, 41, 42).

Conclusions

Occupational exposures are not uncommon in SSc, and the finding of a strong association between male gender and silica or solvent exposure in a predominantly female-driven disease represents an important risk factor that should prompt the attending clinician to find a possible exposure link. Despite the lack of standardised reporting of quantitative exposure information on the study subjects, these studies show an association between silica and solvent exposure and severe SSc disease phenotypes. The association with major organ involvement like cardiac, severe ILD, renal crises and severe gastrointestinal involvement demonstrates higher mortality rates and poorer prognosis. Further research using either a combination of JEMs or blinded expert panels may help to define these

findings in a more standardised manner which will assist many countries to list as an occupational disease and thus be eligible for compensation.

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