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Review

Occupational Exposure to Silica and Autoimmune Diseases: A Systematic Review

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Abstract: Since the first report about the association between occupational exposure to silica and autoimmune diseases more than a century ago, the hypothesis has generated numerous publications but no conclusive statements. This systematic review retrieved 82 epidemiological studies, including cross-sectional, longitudinal, and case-control studies, and 19 studies addressing the possible mechanisms. Major drawbacks include poor assessment of silica exposure, the retrospective nature, the poor quality of a large part of these studies, their limited number for some autoimmune diseases, and the frequent lack of consideration of possible occupational confounders. Nonetheless, the results confirm sufficient evidence for an association between long-term, high-level exposure to silica and the risk of rheumatoid arthritis, scleroderma, and systemic lupus erythematosus, and insufficient evidence for dermatomyositis, Sjögren syndrome, ANCA-positive vasculitis, including Wegener's granulomatosis, and sarcoidosis. The potential mechanisms of such associations are discussed.

Keywords: silica; silicosis; rheumatoid arthritis; scleroderma; systemic lupus erythematosus; dermatomyositis; sjögren syndrome; vasculitis

1. Introduction

A relationship between autoimmune diseases and occupational exposure to silica was first proposed more than a century ago by Bramwell, who observed five stonemasons in a case series of nine scleroderma patients [1]. In 1950, the French rheumatologist Emile Colinet described two cases of rheumatoid arthritis who also had pulmonary opacities and a history of exposure to silica in bagging an abrasive powder [2]. In 1953, Anthony Caplan published the first report about the high prevalence of gross, round pulmonary opacities among Welsh coal miners affected by rheumatoid arthritis [3]. Lung opacities were multiple, with well-defined margins, 0.5–5 cm diameters, spread in both lungs, particularly in the peripheral lung, and with minimal or absent aspects of typical pneumoconiosis [3]. After adjusting for age, years of exposure to silica in subjects with such radiological features did not differ from those of their workmates with massive pulmonary fibrosis not associated with rheumatoid arthritis [4]. Such aspects were more frequent among silica-exposed workers showing immune hyperactivity and the release of cytokines, such as interleukine-1 (IL-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor alpha (TNFa). Together with the macrophage lysosomal lysis due to the contact with the silica particles and the resulting release of leukocyte-activating cytokines, these conditions would generate autoimmune responses in subjects genetically prone to develop rheumatoid arthritis [5]. In another French study, there was a 3% prevalence of exposure to silica among 764 patients with a diagnosis of connective tissue disorders; the most frequent diagnoses were scleroderma or systemic sclerosis, rheumatoid arthritis, and dermatomyositis, and, in all instances, they tended to develop Sjögren syndrome [6]. In 2012, a panel of clinicians and epidemiologists reached a consensus about the link between exposure to crystalline silica and the development of a range of autoimmune disorders [7], based on three positive studies for rheumatoid arthritis and two for

scleroderma, one of which was a meta-analysis. Other studies and clinical reports have focused on Systemic Lupus erythematosus (SLE) and some forms of renal vasculitis, such as Wegener's granulomatosis. However, other clinical and population-based studies did not confirm such associations, possibly because of low statistical power resulting from the rarity of both autoimmune diseases and significantly high-level exposures to silica at the population level [8].

This systematic review updates the status of knowledge linking autoimmune disorders to occupational exposure to silica, explores the potential mechanisms, and provides clues on whether and when to consider their compensation as occupational diseases.

2. Materials and Methods

A search was performed on the PubMed to identify articles published in any language presenting original data or providing mechanistic insights, from inception to 31 January 2025 using the following search string: (silica OR silicon dioxide [Mesh] OR crystalline OR quartz OR pottery OR ceramic* OR sand OR stone OR rock OR dust [Mesh] OR brick OR cement) AND (occupation OR occupational exposure OR construction* OR sandblasting OR mining OR slate mining OR foundry OR quarrying OR concrete working OR glass manufacturing) AND ("Rheumatoid arthritis" OR "arthritis* OR "scleroderma" OR "systemic sclerosis" OR sicca* OR "Systemic lupus erythematosus" OR "SLE" OR "sarcoidosis" OR "dermatomyositis" OR Sjögren* OR Wegener* OR "vasculitis" OR autoimmune diseases [Mesh]) AND Human[Mesh] NOT (asbestos OR children OR mouse OR mice OR animal). Although not precisely an autoimmune disease nor targeting the connective tissue, this review also includes the relationship between occupational exposure to silica and sarcoidosis because of its associations with some immune disorders and disruption of the immune response to still unidentified antigens.

Figure 1 describes the flow chart in agreement with the PRISMA guidelines for reporting systematic reviews [9]. The search retrieved 355 papers; 85 were excluded as irrelevant for this review. After checking the abstracts and the list of references of the remaining articles and the selected studies, two additional cross-sectional, three follow-up, and nine case-control studies were retrieved. A further 150 publications were excluded, including 50 reviews, 84 clinical reports, 16 commentaries, and 33 that (1) did not mention silica (No = 27) or (2) did not assess the risk of autoimmune disease posed by silica/silicosis (No = 2) or (3) were duplicates (No = 2) or (4) which full text was not retrieved (No = 2), leaving 82 original epidemiological studies and 19 mechanistic studies.

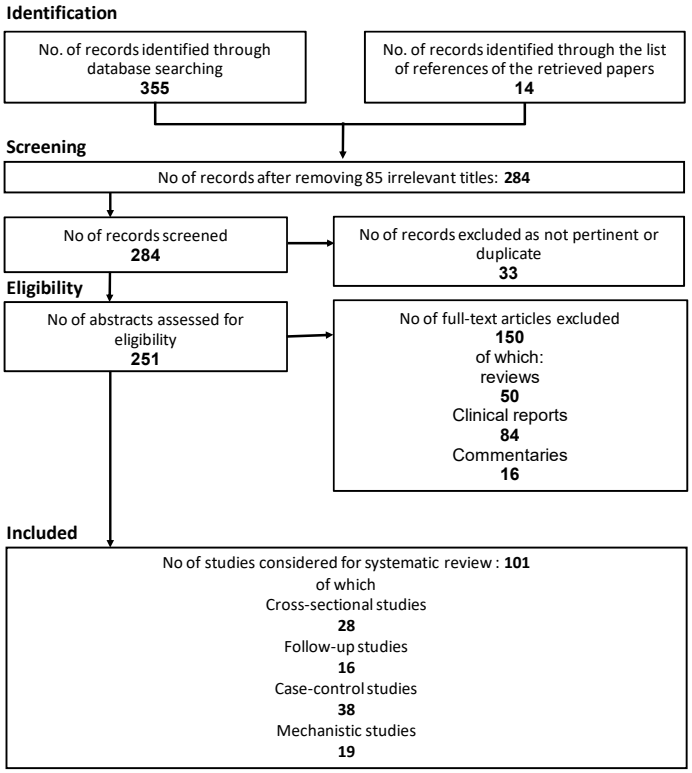

Figure 1. Flowchart of the selection of publications for a systematic review on occupational exposure to silica and autoimmune disorders.

The quality assessment of the epidemiological reports was performed using the NIH tools for cross-sectional and cohort studies and case-control studies [10]. These tools consider, respectively, 13 and 12 items, including the participation rate of the eligible persons, sample size justification, the timing of exposure assessment, length of follow-up, evaluation of dose-response trends, and treatment of confounding variables. Each item requires a binary response. The quality rating in three categories, "Good", "Fair", or "Poor", is the result of the subjective judgment on whether the study results accurately assess an association between exposure and outcome. For this review, complying with less than 50% of the tool requirements was considered indicative of "poor quality", 50–75% indicative of "fair quality", and 75% or more as "good quality".

3. Results

Table 1 shows the main features of the papers selected for this systematic review. The following paragraphs interpret the results of these papers for the most prevalent autoimmune diseases linked to exposure to silica and analyse the overall epidemiological evidence supporting an association.

Table 1. Features and quality assessment of the epidemiological papers on silica and autoimmune diseases selected for review.

Reference Number	First Author	Year	Study Design	Study Size	Control of Confounders	Trend	Exposure Assessment	Autoimmune Outcomes	Association	Quality
54	Freire M	2024	Cross-sectional	255 scleroderma patients	No	No	Job history	Scleroderma	Weak association	Poor
55	Galli G	2024	Cross-sectional	228 scleroderma patients	Sex, age, smoking, residential area	No	Job-exposure matrix	Scleroderma	No association	Poor
16	Blanc PD	2022	Cross-sectional	1988 men from the general population in mining areas	Age, race/ethnicity, and smoking	No	Self-reported occupation	Rheumatoid arthritis	Strong excess risk associated with silica exposure	Fair
17	Schmajuk G	2022	Cross-sectional	2981 men from the general population in mining areas	Age and smoking	No	Self-reported occupation	Rheumatoid arthritis	Strong excess risk associated with silica exposure	Fair
89	Raanan R	2022	Cross-sectional	261 silica exposed workers	No	No	Historical measurements in the workplace	Sarcoidosis, unspecified renal diseases, unspecified autoimmune disorders	increase in risk for unspecified autoimmune disorders	Poor
56	Aguila LA	2021	Cross-sectional	662 scleroderma patients	No	No	questionnaire on occupation	Scleroderma	Association with myopathy in scleroderma patients	Poor
57	Patel S	2020	Cross-sectional	1670 scleroderma patients	Not reported	No	Self-reported silica exposure	Scleroderma	High prevalence of silica exposure	Poor
58	Ballerie A	2020	Cross-sectional	100 consecutive scleroderma patients	No	No	Close-ended questionnaire on silica exposure	Scleroderma	High prevalence of silica exposure	Poor
18	Schmajuk G	2019	Cross-sectional	973 male rheumatoid arthritis patients	Age, ethnicity, smoking, physical strain	No	No	Rheumatoid arthritis	Association with silica and coal mining	Fair
124	Murphy D	2018	Cross-sectional	726 rheumatoid arthritis patients	No	No	Self-reported exposures	Rheumatoid arthritis	The rheumatoid factor was more elevated in patients exposed to dust	Poor
59	Rocha LF	2016	Cross-sectional	947 scleroderma patients	No	No	Clinical anamnesis positive for silica exposure and silicosis	Scleroderma	No association	Poor
60	Marie I	2015	Cross-sectional	142 scleroderma patients	No	No	Expert assessment of the occupational codes	Scleroderma	Association with most severe scleroderma forms	Poor
19	Makol A	2011	Cross-sectional	790 silicotics	Age, race, tipe of trade, tuberculosis, application for compensation	No	Diagnosis of silicosis	Sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, Scleroderma,	All but Sjögren syndrome showed an association with silicosis	Fair

61	Granel B	2008	Cross-sectional	82 scleroderma patients	No	No	Self-reported silica exposure	Sjögren syndrome, ANCA-vasculitis Scleroderma	1/82 cases were exposed to silica	Poor
102	Bartunkova J	2006	Cross-sectional	86 men exposed and 28 never exposed to silica	No	No	Silica measurements in the workplaces	ANCA-positivity (vasculitis)	No association with silica exposure	Poor
62	Magnant J	2005	Cross-sectional	105 scleroderma patients	No	No	Expert assessment on the interview	Scleroderma	Non-significant association with silica exposure	Poor
113	Subra JF	2001	Cross-sectional	58 silicotic patients vs 41 healthy volunteers	No	No	Slate miners	Undefined autoimmune diseases	6/41 autoimmune disease cases; lymphopenia, and elevated T cell count in silicotics	Poor
20	Rosenman KD	1999	Cross-sectional	463 silicotics	No	No	No	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus	All connective tissue diseases exceeded the expectation	Poor
81	Conrad K	1996	Cross-sectional	1. 43 uranium miners with probable/definite SLE and 102 unexposed SLE patients; 2. 1297 uranium miners vs 1000 blood donors	No	Yes	Based on historical measurements	Systemic lupus erythematosus	High titer of SLE-typical antibodies in uranium miners	Poor
90	Falchi M	1996	Cross-sectional	9 pottery workers vs 7 sarcoidosis and 6 haemoptysis patients	No	No	Citology and BAL mineral content	Sarcoidosis	Silica was higher in pottery workers; metals were higher in sarcoidosis	Poor
6	Koeger AC	1995	Cross-sectional	764 patients with connective tissue disease (24 exposed to silica)	No	No	No	Rheumatoid arthritis, scleroderma, systemic lupus erithematosus, dermatomyositis, Sjögren syndrome	Scleroderma was significantly more prevalent among silica-exposed	Poor
63	Conrad K	1995	Cross-sectional	228 possible/definite scleroderma patients, 202 uranium miners, 240 controls.	No	No	Based on historical measurements	Scleroderma	High titer of anti-CENP-B antibodies in miners	Poor
64	Sanchez-Roman J	1993	Cross-sectional	50 workers formerly exposed to silica	No	No	No	Scleroderma, systemic lupus erythematosus, Sjögren syndrome	High prevalence of all CTDs, high frequency of antinuclear antibodies	Poor

49	Rustin MH	1990	Cross-sectional	69 miners and 9 healthy controls	No	No	Job title	Scleroderma	Exposure to silica elicits immune complex and antinuclear antibodies.	Poor
65	Cowie RL	1990	Cross-sectional	24 gold miners	No	No	Job title	Scleroderma	Differences from scleroderma cases in unexposed to silica	Poor
66	Haustein U-F	1990	Cross-sectional	12 scleroderma cases among uranium miners with silicosis	No	No	Historical measurements in the workplace	Scleroderma	High prevalence of scleroderma in silicotics.	Poor
21	Miall WE	1955	Cross-sectional	274 residents in a coal mining area	No	No	Job title	Rheumatoid arthritis	No excess of rheumatoid arthritis among miners.	Fair
79	Walsh SJ	1999	Proportional mortality study	25 U.S. States mortality database	No	No	Expert assessment of the occupational codes	Scleroderma	No association	Fair
91	Iversen IB	2024	Prospective cohort study	Total Danish population	Age, sex, calendar year, education, smoking, connective tissue disease, cancer and medications	Yes	Quantitative job-exposure matrix	Sarcoidosis	Increase in risk with exposure metrics	Good
22	Lee S	2023	Prospective cohort study	98% of the Korean population	Age, sex, insurance type, and household income	No	Self-report of dust-related disease	Rheumatoid arthritis	Significant association	Fair
23	Min JS	2021	Prospective cohort study	150,000 male workers exposed to silica undergoing periodical medical control	Age	Yes	Years of exposure	Rheumatoid arthritis	Significant association, no upward trend	Fair
24	Boudigaard SH	2021	Prospective cohort study	Total Danish population	Age, year of follow-up	Yes	Quantitative job-exposure matrix	Scleroderma, rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis	Significant association, with upward trend for RA and scleroderma but not vasculitis	Good
92	Jonsson E	2019	Prospective cohort study	297,917 Swedish construction workers	Age, smoking	Yes	Job-exposure matrix	Sarcoidosis	Significant association	Good
25	Vihlborg P	2017	Prospective cohort study	2187 male foundry workers	Sex, age, calendar year of follow-up	Yes	Based on historical measurements	Sarcoidosis, serum positive rheumatoid arthritis	Association with silica-related occupations	Fair
26	Blanc PD	2015	Prospective cohort study	240,983 male construction workers	age and smoking	No	Job-exposure matrix	Rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis	Association with silica exposure	Fair
82	Li X	2012	Prospective cohort study	SLE hospitalization in the Swedish population	Age, sex occupation, geographic are, socio-economic status	No	Job title	Systemic lupus erythematosus	Significant association, no upward trend.	Good

27	Li X	2008	Prospective cohort study	28,329 hospital admissions for rheumatoid arthritis	Age, sex occupation, geographic area, socio-economic status	No	No	Rheumatoid arthritis	Significant association	Good
93	Izbicki G	2007	Prospective cohort study	15,083 rescuers of 2001 WTC disaster	No mention	No	No	Sarcoidosis	Increased incidence among gold miners	Poor
28	Steenland K	2001	Prospective cohort study	Health surveillance data of 5086 silica exposed workers	age, sex, race, calendar year of follow-up	Yes	Based on historical measurements	Rheumatoid arthritis	High risk in silica-related occupations	Fair
29	Brown LM	1997	Prospective cohort study	mortality among 1130 silicotics	age, sex, race, calendar year of follow-up	No	Based on the diagnosis of silicosis	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus	Significant association with upward trend	Good
30	Steenland K	1995	Prospective cohort study	3328 gold miners	age, sex, race, calendar year of follow-up	No	Based on historical measurements	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus	Significant association, upward trend	Good
31	Lundberg I	1994	Prospective cohort study	375,035 men and 140,139 women from the Swedish census	Age and sex	No	Job title	Rheumatoid arthritis	Increased incidence after WTC dust exposure	Fair
32	Klockars M	1987	Prospective cohort study	1026 granite quarry workers	Age	No	Based on historical measurements	Rheumatoid arthritis	Significant association	Fair
67	Cowie RL	1987	Prospective cohort study	95,000 South African gold miners	No	No	Job title	Scleroderma	Significant excess incidence of scleroderma; cases did not differ in years of exposure and prevalence of silicosis.	Good
33	Sigaux J	2023	Case-control	97 RA cases and 308 controls	age, sex, disease duration, ACPA)/RF positivity and smoking	Yes	Questionnaire-based score	Rheumatoid arthritis	High risk for cleaning and exposure to dusty clothes, no trend.	Fair
34	Cavalin C	2023	Case-control	100 scleroderma cases, 97 RA cases, 774 population controls	age, sex, smoking	No	Questionnaire-based score	Scleroderma, rheumatoid arthritis	Association of scleroderma and rheumatoid arthritis with occupational silica exposure	Fair
35	Wrangel O	2021	Case-control	17,353 RA cases and 34,706 controls	No	Yes	Job-exposure matrix	Rheumatoid arthritis	Association with silica exposure in men	Fair
94	Graff P	2020	Case-control	3663 sarcoidosis cases and 7326 controls	Matching by age, sex and county of residence	yes	Job-exposure matrix	Sarcoidosis	Significant association, inconsistent trend	Poor
95	Beijer E	2020	Case-control	256 sarcoidosis patients and 73 controls with obstructive sleep apnea	No	No	Job-exposure matrix	Sarcoidosis	Lack of an association	Poor
36	Ilar A	2018	Case-control	3522 cases of rheumatoid arthritis and 5580 controls	age, sex, education, BMI, smoking, alcohol, environmental exposures	No	Expert assessment on occupational codes	Rheumatoid arthritis	Association with jobs implying exposure to silica	Fair
98	Chaigne B	2015	Case-control	175 cases of Sjögren syndrome and 350 controls	Matching by age and sex	No	Expert assessment on job titles	Sjögren syndrome	Lack of an association	Fair
101	Stamp LK	2015	Case-control	49 cases of vasculitis and 196 controls	Not clarified	No	Job title	Wegener's vasculitis	Association with silica exposure	Poor

37	Yahya A	2014	Case-control	149 male cases of rheumatoid arthritis and 213 male controls	Matching by age, sex, and residence, adjustment by smoking	No	Self reported	Rheumatoid arthritis	Association with ACPA-positive rheumatoid arthritis among exposed to silica	Fair
68	Marie I	2014	Case-control	100 scleroderma cases and 300 controls	No	Yes	Expert assessment on occupational codes	Scleroderma	Significant association	Fair
38	Stolt P	2010	Case-control	577 cases of rheumatoid arthritis and 659 controls	Age, sex residence, social class, smoking, osteo-articular traumatisms, physical activity	No	Self reported	Rheumatoid arthritis	Association with ACPA-positive rheumatoid arthritis	Poor
39	Cooper GS	2010	Case-control	258 cases of systemic lupus erythematosus and 263 controls	Matching by age, sex, and geographical area	Yes	Expert assessment on occupational histories	Antinuclear antibodies titer	Significant association	Fair
99	Knight A	2010	Case-control	2288 cases of Wegener's vasculitis and 22,880 controls	Matching by age, sex, residence, and marital status	No	Based on job title	Wegener's vasculitis	No association	Fair
40	Gold LS	2007	Case-control	52,919 cases of autoimmune diseases and 264,569 controls	Age sex, race, education, residence area, socio-economic status	No	Expert assessment on occupational codes	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus	No association	Good
103	Hogan SL	2007	Case-control	120 ANCA vasculitis patients and 109 controls	Age sex, state of residence	Yes	Expert assessment on job titles	ANCA vasculitis	Significant upward trend	Fair
41	Finckh A	2006	Case-control	95 cases of systemic lupus erythematosus and 191 controls (African-American women)	Number of pregnancies, smoking, education.	Yes	Expert assessment on occupational histories	Systemic lupus erythematosus	Significant association	Fair
119	Cooper GS	2006	Case-control	21 subjects from the general population with high ANA titer vs 245 with low ANA titer.	Age, sex and race	No	Expert assessment on occupational history	Antinuclear antibodies titer	Non significant association	Fair
42	Stolt P	2005	Case-control	276 Rheumatoid arthrits cases and 276 controls	Age, sex residence, smoking	No	Self reported	Rheumatoid arthritis	Significant association	Fair
104	Beaudreuil S	2005	Case-control	60 ANCA-positive patients and 120 hospitalized controls	Matching by age and sex	yes	Expert assessment on occupational history	ANCA vasculitis	Significant association	Fair
69	Bovenzi M	2004	Case-control	55 scleroderma cases and 171 controls	Age, and sex	No	Expert assessment on occupational history	Scleroderma	Non significant association among women	Fair
70	Maître A	2004	Case-control	93 cases (83 women) and 206 controls(166 women)	Matched by age and sex, adjusted by education	No	Expert assessment on occupational codes	Scleroderma	No association	Fair

43	Calvert GM	2003	Case-control	194–970 cases and 396,481–1,964,005 controls (24 U.S. States death certificates)	Age, birthplace, education, and smoking	Yes	Expert assessment on occupational codes	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus, sarcoidosis	Association with rheumatoid arthritis, but not scleroderma, Systemic Lupus Erythematosus, or sarcoidosis	Good
105	Lane SE	2003	Case-control	75 vasculitis patients and 273 hospital controls	Age and sex matching; adjusted by residence, occupations, solvent exposure, allergy, farm work, and smoking.	No	Job-exposure matrix	Vasculitis	Borderline association	Fair
71	Diot E	2002	Case-control	80 scleroderma cases and 160 hospital controls	Matching by age, sex, and smoking	Yes	Expert assessment on occupational codes	Scleroderma	Significant association	Fair
72	Thompson AE	2002	Case-control	67 scleroderma cases and 87 controls	Age and sex matching	No	Self reported	Scleroderma	No association	Poor
83	Parks CG	2002	Case-control	265 cases of systemic Lupus Erythematosus and 335 controls	Age, sex, race, education, state of residence, farm work	Yes	Expert assessment on occupational codes	Systemic lupus erythematosus	Significant association	Poor
118	Stratta P	2001	Case-control	31 cases of mixed vasculitis and 58 hospital controls	Matching by age, sex, and residence area	No	Self reported	ANCA vasculitis	Significant association	Fair
73	Bovenzi M	2001	Case-control	76 Scleroderma cases and 171 hospital controls	Matching by age, sex,and date of dismissal; adjusted by smoking, alcohol, use of medication, and pets	No	Expert assessment on occupational codes	Scleroderma	Non significnt increase in risk among women	Fair
46	Turner S	2000	Case-control	58 rheumatoid arthritis cases and 232 controls	Matching by age, sex, year of starting employment; adjustment by smoking and coal mine work	Yes	Based on historical measurements	Rheumatoid arthritis	No association	Fair
74	Englert H	2000	Case-control	160 scleroderma cases and 83 controls	age, socio-economic status	No	Expert assessment on occupational codes	Scleroderma	Significant association	Poor
96	Rafnsson V	1998	Case-control	8 cases of sarcoidosis and 70 controls	No	No	Personal workplace measurements	sarcoidosis	Significant association	Fair
75	Burns CJ	1996	Case-control	274 female scleroderma cases and 1184 female controls	No	No	Self reported	Scleroderma	No association	Poor
76	Bovenzi M	1995	Case-control	21 scleroderma cases and 42 hospital controls	Matching by age, sex and date of hospital dismissal	No	Expert assessment on occupational history	Scleroderma	Significant association	Fair
100	Nuyts GD	1995	Case-control	16 cases of Wegener's and 32 controls	Matching by age, sex, and residence area	No	Self reported	Wegener's vasculitis	Significant association	Poor

77	Silman AJ	1992	Case-control	56 scleroderma cases and 97 controls	No	Yes	Expert assessment on occupational codes	Scleroderma	No association	Poor
45	Sluis-Cremer GK	1986	Case-control	157 Rheumatoid arthritis cases and 157 controls	Matching by age and sex	No	No	Rheumatoid arthritis	Association with silicosis	Fair
78	Sluis-Cremer GK	1985	Case-control	79 scleroderma cases and 79 controls in a miners	Matching by year of birth	Yes	Based on historical measurements	Scleroderma	No association with silicosi; association with cumulative silica exposure	Fair
4	Miall WE	1953	Case-control	20 male cases of rheumatoid arthritis patients with silicosis vs 60 male controls with RA but not silicosis	Age	No	No	Rheumatoid arthritis	Significant association among coal miners	Fair

3.1. Rheumatoid Arthritis

Approximately 15–58% of rheumatoid arthritis patients show radiological features of interstitial pulmonary disease [11], and the genetic polymorphisms in these patients have multiple similarities with familial pulmonary fibrosis [12]. On the other hand, the heritability of genetic traits accounts for 60% of cases, with an 11–37% contribution from the HLA types of cell membrane receptors [13]. Numerous clinical reports have described unusual occurrences and unexpected excess cases of rheumatoid arthritis among subjects exposed to environmental factors, starting from Caplan's syndrome description among Welsh coal miners [3]. However, the nature of such observations still appears controversial because of the uncertainty of the silica exposure level [14] or the nature of Caplan's syndrome, whether a specific nosological entity, a form of silica-related sarcoidosis, or the simple chance co-occurrence of silicosis and rheumatoid arthritis [15].

The search conducted for this review identified seven cross-sectional studies, four of which were positive for an association with silica exposure, one for silicosis, and two did not support an association [6,16–21]. None of these studies reached a good quality level, mainly because the authors did not mention exposure assessment or relied on the self-reported job (2/4 positive and 1/2 negative studies). Although important from the hypothesis-generating perspective, the results of retrospective and cross-sectional studies do not allow for conclusive statements about the observed associations. Based on those results, it remains unclear whether the appearance of interstitial lung disease in silica-exposed workers suffering from rheumatoid arthritis results from silica causing both diseases or if the autoimmune disease itself causes the interstitial lung disease, then aggravated by the exposure to silica. The evidence from more formal study designs, such as high-quality cohort and case-control studies, along with solid mechanistic evidence, is decisive.

Eleven cohort, and 12 case-control studies investigated the association between rheumatoid arthritis and silica. Four prospective cohort studies scored as good- and seven as fair-quality publications; all the results were positive for a significant association with workplace silica concentration, silica exposure assumed by applying job-exposure matrices, silica-related occupations, or a previous diagnosis of silicosis [22–32]. Four studies explored trends with some indicator of silica exposure; three scored as good quality and observed a significant upward trend in the risk of rheumatoid arthritis [24,29,30]. Another fair-quality study did not observe an upward trend in risk [23]. This cohort study included almost 150,000 Korean workers undergoing periodical medical controls because of their exposure to silica and relied on years of silica exposure as the exposure metric. As for the 12 case-control studies [4,33–46], only two, both based on the U.S. states' mortality database, scored as good-quality studies; both were based on large numbers and applied job-exposure matrices to classify jobs according to probability and intensity level of silica exposure. The results were contrasting, possibly due to the different approach: one was a traditional case-control analysis of 52,919 cases of autoimmune diseases, including rheumatoid arthritis, scleroderma, and Systemic Lupus Erythematosus, and 264,569 controls showing no association [40], and the second was a mortality odds ratio analysis yielding the opposite finding but an inverse trend in risk of rheumatoid arthritis [43]. All the other case-control studies but one scored as fair-quality; 8 out of 9 of these studies observed an association with various metrics of silica exposure or surrogates, such as a silica-related job title, self-reported exposure, job-exposure matrix, or expert assessment based on questionnaire responses or job titles. The only case-control study with a low-quality score was also positive for an association [38]. The four high-quality prospective cohort studies were heterogeneous in the outcome (two mortality studies, one follow-up of the incidence of rheumatoid arthritis and scleroderma among the entire Danish population, and one study of hospital admissions), in the exposure metrics (in one study it was the occupation as a miner or quarryman, in another a previous diagnosis of silicosis, in the third historical silica measurements were available, and, in the Danish study, a quantitative job-exposure matrix assigning a level of respirable crystalline silica was applied), and in the study size, ranging 1130–28,329. Being aware of such limitation, we explored the effect size with a meta-analysis (https://metaanalysisonline.com). Following the Cochrane Handbook, studies using a different study design (case-control and cross-sectional studies) were excluded due to their variable susceptibility to bias [44]. Based on a random effect model, the effect estimate was 2.28 (95% CI 1.41–3.71), which would result in an attributable fraction of 56% (95% CI 29–73) for the scleroderma cases occurring among workers exposed to silica. Considering that the employed in the mining industry account for 0.08% of the world population of working age, with only a tiny minority of women, the silica-attributable fraction at the population level would be almost negligible; however, this does not diminish the occupational relevance of the few cases observed among the silica-exposed workforce.

The overall epidemiological evidence seems overwhelmingly supportive of an increase in the risk of rheumatoid arthritis associated with high-level, prolonged exposure to silica. A contribution of genetic factors is

suggested by an accelerated progression of the radiological features of silicosis, as well as a higher prevalence of "*r*" nodules, according to the ILO classification, among those with rheumatoid arthritis [45]. Also, years and level of exposure to silica were lower among 58 cases of rheumatoid arthritis among ceramic and sandstone workers undergoing workplace health screenings in Stoke-on-Trent, U.K., compared to 232 controls, engaged in the same jobs, free from rheumatoid arthritis symptoms [46]. Also, a few studies suggested a possible interaction between smoking [26,33] and exposure to total dust, the silica content of which may vary substantially, contributing to the occurrence of a range of autoimmune diseases, including rheumatoid arthritis. If so, the generic inflammatory reaction following dust exposure, instead of the specific silica-related toxicity, would explain the excess incidence of rheumatoid arthritis in dusty trades.

3.2. Scleroderma

Scleroderma, or systemic sclerosis, is an autoimmune disease that features progressive fibrosis in the skin, endothelia, and internal organs, with inflammation and the presence of auto-antibodies specific to its diverse forms. It is also a complex, multifactorial disease typically more frequent among women, with multiple genes involved, each carrying a modest increase in risk, and in which several environmental factors, including drugs and occupational exposure to physical and chemical agents, might intervene, modulating the immune response [47]. The peculiar observation of 17 scleroderma cases among male South African gold miners initiated research into the link between scleroderma and silicosis, called Erasmus syndrome for the author who first described it [48].

Apart from the co-occurrence of the two diseases, no other clinical, radiological, or histological peculiarities help to discriminate the scleroderma cases observed among silica-exposed workers from workmates unaffected by scleroderma [49]. However, the combination would not be a random event but would result from silica cytotoxic suppression of cellular immunity. Immune suppression would also be responsible for the autoimmune reactions and formation of circulating immuno-complexes. In genetically prone individuals, silica particles in various tissues would trigger fibroblast proliferation and the consequent development of scleroderma [50]. In vitro experiments showed that adding silica to cultured fibroblasts from skin biopsy in 96 scleroderma patients and 104 controls modified the expression of six genes associated with the risk of scleroderma, including a reduction in MMP3 and an increase in COL3A1 expression [51]. An exceptionally high frequency of two HLA-D polymorphisms was reported in 27 German uranium miners suffering from scleroderma and exposed to high silica levels, which together with the exposure to external factors, would promote the synthesis of anti-Scl-70 antibodies, which, in turn, increase the susceptibility to develop scleroderma [52]. High-level exposure to silica, more than silicosis, would be the determining factor [53]. We identified 17 cross-sectional, 5 cohort, 14 case-control studies [6,19,20,24,26,29,30,34,40,43,54–78], and one proportionate mortality study [79]. Only one out of the 17 cross-sectional studies scored "fair" in quality, and its results were positive for an excess prevalence of scleroderma among silicotics [19]; the score was "poor" for all the others. One of the 16 poor-quality studies only compared the clinical severity of scleroderma in silica-exposed vs. unexposed, whilst 13/15 of the other studies reported positive findings. A major issue in these studies was the inaccuracy in defining exposure to silica: four did not even mention exposure assessment, one used the occupational title reported in the clinical anamnesis, seven relied on self-reported information (current job, job history, or close listing of occupational exposures), two were based on expert assessment on the occupational codes, and only one relied on historical workplace measurement of airborne silica.

Case-control studies provide inconsistent results [34,40,43,68–78]: six (5 good- and one poor-quality) were positive for an association with silica exposure vs. 8 (2 good-, 3 fair-, and 3 poor-quality) that failed to detect the association. In 10 instances, the assessment of exposure to silica relied on the expert evaluation of the work histories or occupational codes: of these, four studies showed an association, and six did not. The only proportionate mortality study, based on the occupational code reported in the death certificates of 29 U.S. States, also did not support an association [79].

On the contrary, all five cohort studies reported an excess risk of scleroderma among workers exposed to silica [24,26,29,30,65]; four out of five had a "good" score in quality; the study size was large in three (total Danish population [24], about 241,000 construction workers [26], and 95,000 South-African gold miners [65]); and the other two relatively smaller-size studies relied on historical workplace measurements [30] or the diagnosis of silicosis [29]. The follow-up study of South Dakota gold miners jointly explored the risk of scleroderma and systemic lupus erythematosus; being aware of this limitation, we included the reported risk estimate in the meta-analysis of both diseases because of its informative value. The two relatively small cohort studies and the large Danish study analysed the dose-response relationship and reported a significant upward trend with silica exposure metrics. The meta-analysis of the four good-quality cohort studies resulted in a summary estimate of 7.02 (95%

CI 1.62–30.4), with significant heterogeneity across studies because of the inconsistent magnitude of effects. Although based on a limited number of studies and with a wide confidence interval, the effect size seems large enough to assume causality.

Still, the evidence from case-control studies is inconsistent with the results from cross-sectional and cohort studies. Besides, the use of hand vibrating tools is common among silica-exposed workers, who tend to develop hand-arm vibration syndrome (HAVS), with the Raynaud phenomenon of one or more fingers (white finger) and damage to the small joints and the peripheral nerves of the upper limbs. During the detection of spasms in the peripheral arteries in silica-exposed workers, an accurate diagnostic work-up should be developed to exclude HAVS and silica-related scleroderma. This might be irrelevant from the compensation perspective, but important from the preventive point of view. Notably, occupational exposure to silica appears to be associated with more severe forms of scleroderma, with widespread skin involvement, interstitial lung disease, generalized microangiopathy with digital ulcers, cardiomyopathy, and the appearance of neoplasms [59].

3.3. Systemic Lupus Erythematosus (SLE)

A review on the aetiology of Systemic Lupus Erythematosus (SLE) concluded that this autoimmune disease also results from the interaction between multiple genetic and environmental factors; occupational exposure to silica, smoking, and disruption of hormonal balance would be especially relevant, while alcohol would be protective [80]. We identified 14 studies: five cross-sectional, four case-control, and five cohort studies [6,19,20,24,26,29,30,40,41,43,64,81–83]. Apart from two case-control studies, which had good quality [41,45], the other studies reported an association with occupational exposure to silica. Only one cross-sectional study included historical measurements [80] vs. four that did not even mention exposure assessment [6,19,20,64]. As for the five cohort studies, two relied on job-exposure matrices [24,26], one used job titles [82], one was a cohort of silicotic patients [29], and one used historical workplace measurements of airborne silica [30]. As mentioned above, this last cohort study explored the risk of systemic lupus erythematosus jointly with scleroderma, and we decided to keep it for a tentative meta-analysis because of its good quality and informative value, together with two other good-quality cohort studies. With the due concern about the heterogeneity of exposure metrics, based on having held the job title of miner/quarryman in two consecutive population censuses [81], having been hospitalised for silicosis [29], or historical silica measurements in South Dakota gold mines [30], the summary estimate was 6.28 (95% CI 2.10–18.8), with a wide confidence interval and a significant heterogeneity across studies because of the inconsistent magnitude of effects. Only one case-control study explored trends by metrics of occupational exposure to silica [41]; a significant upward trend in SLE risk was observed by years of exposure. This study was conducted among women in the Boston, MA, area and included mostly African American women. The risk estimates were adjusted by parity, smoking, and education, none of which was related to SLE risk or silica exposure. Exposure to silica occurred in jobs such as making ceramic moulds in dental laboratories, working at construction sites where sandblasting occurred (bystander exposure), or as a custodian using scouring powders [41]. Although such jobs might involve substantial exposure to silica, with a few cases of silicosis reported [84], the top category of years of exposure was 5 or more years, and it seems unlikely that those exposures might be comparable to those traditionally bearing an elevated risk of silicosis. Besides, a relatively recent review of the published reports on silica and SLE risk, combining studies conducted with different study designs, suggested publication bias [85], a further reason for concern in interpreting epidemiological results. Therefore, uncertainty remains about the nature of the observed association and whether unaccounted confounders, typical of low socio-economic status, might account for the positive findings.

3.4. Sarcoidosis

Sarcoidosis is a multisystemic disease, characterized by the appearance of non-caseous granulomas and the histological finding of CD4+ T lymphocytes surrounding epithelioid cells, multinuclear giant cells, and macrophages [86]. A credible aetiological hypothesis calls for a cell-mediated response to an unknown antigen led by T-helper CD4+ cells that proliferate and trigger the inflammatory cascade and macrophage activation. This process would lead to granuloma formation and, in some instances, might evolve towards fibrosis. The limited number of receptors expressed on the surface of CD4+ T lymphocytes would suggest that such an immune response is specific to one or a few antigens [86]. Micronodular opacities are spread in the lung parenchyma, especially in the upper and middle lobes, and are accompanied by mediastinal lymphadenopathy [87]. The respiratory function tests and the lung diffusion capacity are frequently normal, and the broncho-alveolar lavage might show lymphocytosis and an increase in the number of CD4+ T-cells and the CD4/CD8 ratio [86].

Crystalline silica and other environmental pollutants might be capable of activating innate immunity through the link between the cell membrane Toll-like receptors (TLR) and cytoplasm receptors on one side, and the nucleotide-binding oligomerization domain-like (NOD-like) receptors (NLR) on the other side. Such immune events are also typical of sarcoidosis [88].

This systematic review identified three cross-sectional, four cohort, and four case-control studies addressing the association between occupational exposure to silica and the risk of sarcoidosis [19,25,43,89–96]. Two good-quality cohort studies suggested a positive association [91,92] while two case-control studies, one with good quality and another with poor quality, did not [43,95]. Overall, the study quality was scored as poor in 5 studies (two cross-sectional, one cohort, and two case-control studies), and, apart from the follow-up of the 2001 New York World Trade Centre disaster rescuers [93], the exposure was reasonably assessed. An upward trend was reported in the Danish cohort study [91], in an Icelandic study [96], and in a Swedish cohort of iron foundrymen [25], although based on small numbers, but not in another two papers [43,94]. Cross-sectional results suggested an association in two out of three studies [19,89,90], whilst the results of case-control studies were inconsistent [43,94–96].

Notably, the mean exposure levels among Swedish foundrymen were lower than the tolerance limit value for occupational exposure to silica [25], unlikely to convey an increase in the probability of developing silicosis, as was the case in a cross-sectional study of 261 hospital admissions of silica-exposed workers in an Israelian hospital [89].

The inconsistent results of the few dose-response analyses conducted thus far, the similar average exposure to silica among cases of sarcoidosis compared to their workmates, and a few clinical reports about sarcoidosis following accidental acute events following exposure to very high levels of dust or toxic chemicals [93,97], suggest that the observed relationship with silica would result from an unspecific reactive mechanism in response to acute events instead of chronic cumulative exposures.

3.5. Other Autoimmune Disorders

Other autoimmune disorders less frequently investigated for a possible association with occupational exposure to silica include dermatomyositis (two studies) [6,26], Sjögren syndrome (four studies) [6,19,64,98], Wegener's granulomatosis, a systemic autoimmune vasculitis frequently targeting the kidney (three studies) [99–101], and other forms of vasculitis associated or not with specific autoantibodies (eight studies) [19,24,46,102–105].

Dermatomyositis was explored in a poor-quality cross-sectional study that explored multiple autoimmune disorders (N = 764), including 24 cases among silica-exposed workers [6]; three dermatomyositis cases (12.5%) were observed among the 24 autoimmune disorders in silica-exposed patients and 22 (2.9%) among the 740 silica-unexposed patients. The second was a fair-quality follow-up study of a large cohort of Swedish construction workers that detected 27 cases of autoimmune disorders but did not specifically explore the association of dermatomyositis with silica exposure. However, using the data provided in the paper, the crude incidence rate was calculated to be 8 per 1,000,000 vs. a reported incidence of 1.1 per 1,000,000 among the general Swedish population [106].

Sjögren syndrome and its association with occupational exposure to silica was the object of four studies: three poor-quality cross-sectional studies [6,19,64] and one fair-quality case-control study [98]. In three out of these four studies, the results did not support an association; in a small cross-sectional study of 50 workers formerly exposed to silica, the proportion of three connective tissue diseases, including Sjögren syndrome, was reportedly elevated, but no comparison with a reference unexposed population was made.

The three case-control studies that investigated the risk of Wegener's granulomatosis associated with occupational exposure to silica had inconsistent findings. However, the quality was poor in two and fair in the third study, and the one that concluded positively for an association relied on 16 cases and 32 controls, too small a study size to support the hypothesis [100]. Another seven studies relied on a generic definition of vasculitis. Among this group, three case-control [46,102,104] and one cross-sectional study [19] investigated the risk of developing anti-neutrophil cytoplasm antibodies (ANCA), typical of the ANCA-positive vasculitis group, which includes Wegener's syndrome; their results were consistently positive for an association, contrasting the opposite findings of a poor-quality cross-sectional study [102]. Another study combined 75 cases of primary systemic vasculitis, including 47 cases of Wegener's granulomatosis; in this study, silica exposure was a significant risk factor for all forms of vasculitis combined (OR = 3.0, 95% CI 1.0–8.4) and particularly ANCA-positive vasculitis (OR = 4.9, 95% CI 1.3–18.6) but not Wegener's granulomatosis (OR = 2.5, 95% CI 0.8–8.5) [105]. Although risk did not increase with the duration of exposure to silica, the risk of all forms of vasculitis combined associated with silica-related jobs lasting 40 or more years was increased 2.6-fold (95% CI 1.03–6.73).

Finally, a study of multiple autoimmune outcomes associated with occupational exposure to silica also explored the risk for small vessel vasculitis, and found a significant risk but inconsistent trends according to the exposure metrics [24].

6. Discussion

The first reports of autoimmune diseases in silicotic workers suffering from silicosis date back to the middle of the past century and have been increasing in the past decades, possibly as a result of a longer life expectancy in the general population and the improved survival of silicotic patients [107]. However, the results of the epidemiological studies identified for this systematic review provide evidence of a significant increase in the risk of rheumatoid arthritis, scleroderma, and systemic lupus erythematosus. The positive findings in studies supported by high-quality exposure assessment, i.e., based on workplace measurements or a clinical diagnosis of silicosis, strengthen the evidence for association. The evidence seems contradictory for sarcoidosis, while the number of studies focusing on dermatomyositis, Sjögren syndrome, and Wegener's granulomatosis are quantitatively and qualitatively insufficient to formulate any conclusive statement (Table 2).

Table 2. Summary table of the epidemiological results on the link between occupational exposure to silica and the development of autoimmune disorders.

Autoimmune Disease	Overall Evidence from Prospective Cohort Studies	Overall Evidence from Case-Control or Cross-Sectional Studies	Evidence by the Quality of Exposure Assessment			Confounders and Interpretative Limitations
			High	Medium	Low	
Rheumatoid arthritis	[sufficient] 11/11	[sufficient] 14/19	8/9	8/9	10/12	Use of vibrating tools, manual material handling, smoking, poor exposure assessment, non-specific association
Scleroderma	[sufficient] 5/5	[Limited] 21/31	6/6	9/17	10/13	Low statistical power, methodological issues, use of vibrating tools, smoking
SLE	[sufficient] 5/5	[Limited] 7/9	5/5	4/6	3/3	Poor exposure assessment, unclear role of smoking (interaction?)
Sarcoidosis	[Poor] 2/4	[Poor] 4/7	4/4	3/5	1/2	Unclear confounding role of smoking, diagnostic imprecision
ANCA-positive vasculitis (incl.Wegener's)	[no studies]	[Poor] 5/10	1/2	3/4	3/4	Low statistical power, limited number of studies
Sjogren's syndrome	[no studies]	[Poor] 1/4	0/1	0/1	1/2	Insufficient number of studies, large prevalence of negative findings
Dermatomiositis	[Poor] 1/1	[Poor] 0/1	0/0	1/1	0/1	Insufficient number of studies

Most occupations involving exposure to silica are physically demanding because of the repeated handling of heavy loads and prolonged exposure to incongruous postures. Such conditions might accelerate the ageing process and result in chronic inflammation of the joints, which autoimmune reactions might superimpose and pave the way to the clinical appearance of connective tissue disorders. Understanding whether physical strain and/or HAV might act as confounders of the observed associations would be relevant for correctly addressing preventative interventions, though irrelevant from the compensation perspective.

Nonetheless, silica is one of the environmental substances capable of affecting the immune system and eliciting autoimmune diseases in the exposed [108]. According to some authors, silicosis itself might be considered a connective tissue disease because of its ability to induce the formation of fibro-hyaline tissue following the activation of both the Innate and Adaptive Immunity as a result of the release of cytokines by silica-activated macrophages [109]. As shown in Japanese brickyard workers diagnosed with pneumoconiosis [110], producing autoantibodies against the Fas/CD95 death receptor and related molecules would induce autoimmune reactions [108]. Changes in the number or functions of CD4+ CD25+ regulatory T-lymphocytes may also promote autoimmune reactions [111]. Interestingly, after adjusting for age, peripheral blood mononuclear cells were proportionally more frequent in silicotic patients than in healthy individuals [112], with an increase in the proliferation of responder T-lymphocyte (CD4 + CD25- cells). The increase in activated T-lymphocytes contrasts with the decrease in total lymphocytes, which is consistent across sub-populations, whether B, T, or NK cells [113], including regulatory T-cells in a dose-related fashion with the level of silica exposure [114]. The expression of cytotoxic T lymphocyte antigen-4 (CTLA-4) on CD4 T cells and programmed cell death protein-1 (PD-1) in CD4 and CD8 cells was significantly lower in silica-exposed subjects with no radiological signs of silicosis

compared to unexposed referents [115]. Both molecules are important down-regulators of immune responses and so maintain self-tolerance. CTLA-4 limits the immune response by releasing signals that induce the antigen-specific apoptosis of activated T cells and suppress the proliferation of T lymphocytes. Such down-regulation prevents self-reactive T lymphocytes from inducing autoimmune diseases; conversely, the decreased CTLA-4 expression in CD4 T cells of silica-exposed individuals would allow survival of autoreactive T lymphocytes and the consequent development of autoimmune diseases [115]. Such an enhanced self-destructive response is accompanied by increased serum levels of soluble IL-2 receptor (sIL-2R), the pro-inflammatory (IFN-γ, IL-1α, TNF-α, IL-6) and anti-inflammatory (IL-10 and TGF-β) cytokines, and decreased IL-2 levels [116]. A somewhat different profile of cytokines was observed among cement mason apprentices exposed to silica in the State of Washington, U.S.A. [117], who had higher serum levels of cytokines (IL-1b, IL-2, Il-4, IL-10, and IFN-γ) and lower expression of CD25+ and CD69+ surface antigens [117]. Besides, IL-12 and reactive oxygen species were released in *in-vitro* cultures of macrophages following treatment with amorphous and crystalline silica [118]. Such changes in the circulating cell level translate into the detection of high serum levels of autoantibodies in silica-exposed workers, such as antinuclear (ANA) [63,119–122], extractable antinuclear (ENA) [122], anti-DNA [119], and anti-myeloperoxidase-specific (MPO) peripheral anti-neutrophil cytoplasmic antibodies (pANCA) [121]. Results are inconsistent about the anti-citrullinated antibodies (ACPA) in silica-exposed workers. These are detected in the majority of rheumatoid arthritis as a result of the conversion of arginine residues along some protein chains into citrulline in the inflammation process, thus not being recognized as self and generating the autoimmune response [123]. ACPA antibodies were not detected in U.K. patients with rheumatoid arthritis with heterogeneous, generic exposure to external agents, such as vapor, gas, dust, or fumes [124], whilst they were in a Swedish trial including construction and cement workers, who run an excess risk or rheumatoid arthritis independent on ACPA-antibody positivity [36], and a parent study in Malaysia [38]. These studies also observed contrasting findings on the role of tobacco smoking [36,37,124]. Inconsistent results on ANA antibodies and rheumatoid factor (RF) were also published in 78 Iranian silica-exposed workers, including 10 with radiological signs of silicosis and two RF positive: the prevalence of RF positivity and ANA antibodies did not vary between subjects with vs. without silicosis [125]. A Turkish study explored the role of oxidative stress in the etiology of silicosis and silica-associated autoimmune diseases by measuring biomarkers related to oxysterols, which are 27-carbon end products of cholesterol oxidation, also implicated in the etiology of atherosclerosis and other inflammatory and degenerative diseases [126]. Biomarkers included 8-isoprostane, 4-hydroxynonenal (4-HNE), and malon-dialdehyde (MDA), all values of which were significantly elevated in patients with silicosis, suggesting a contribution of lipid oxidation in the etiology of silicosis and the associated autoimmune diseases [126].

This systematic review also highlights a few drawbacks in the existing epidemiological literature, associating the risk of autoimmune diseases with exposure to silica or silicosis, which limits the interpretation of results. Publication bias has been suggested in two reviews on silica exposure and the risk of SLE [84], and rheumatoid arthritis [127] which also highlighted the potential recall bias, misclassification bias in some instances of self-report of the disease, selection bias in the studies based on voluntary participation, and the frequent weakness of the exposure assessment [84,127]. However, good-quality prospective cohort studies consistently reported a positive association with the risk of rheumatoid arthritis, scleroderma, and systemic lupus erythematosus, and selection bias was excluded in a systematic review on scleroderma and occupational silica exposure [128], and dubious in a systematic review on vasculitis [129]. Other interpretative concerns are motivated by the small number of studies for specific autoimmune diseases, the small study size in numerous publications, and the limited number of good-quality studies. The interaction between silica exposure and smoking has been the object of three studies of silica and rheumatoid arthritis and two SLE studies with contrasting findings; future prospective studies are warranted, addressing the possible sources of bias and the role of smoking in the association between silica exposure and connective tissue diseases.

The frequent cross-sectional approach is also concerning as it exposes the risk of reverse causation. A cross-sectional study explored the silicosis-rheumatoid arthritis comorbidity from the reverse perspective in coal miners [130]. In this study, the frequency and severity of radiological silicosis in 100 Pennsylvania coal miners with a diagnosis of rheumatoid arthritis were what was expected from literature data, and the serum immunoglobulin profile in a subset of these patients did not differ from a matched group of rheumatoid arthritis non-miner patients [130]. While relying mainly on the results of well-conducted prospective cohort studies, these results suggest that reverse causation was not a major problem in cross-sectional studies of autoimmune diseases among silica-exposed workers.

5. Conclusions

While mechanistic studies provide generic evidence of the plausibility that occupational exposure to silica, with or without the development of silicosis, might promote the development of autoimmune disease in genetically prone subjects, the epidemiological studies conducted thus far provide variable levels of evidence for the various specific disorders. Based on the consistent results of good-quality prospective studies, the evidence for an association appears sufficient for rheumatoid arthritis, scleroderma, and SLE. Some concerns still exist about the possible confounding role of concurrent workplace exposures, especially physical strain.

In the 1990s, following the appearance of a few cases of scleroderma among male miners, a member addressed the provincial parliament of Ontario, Canada, requesting the Industrial Disease Standards Panel (IDSP) of Canada to assess the evidence for an occupational connection [131]. However, Canada did not compensate occupational cases of scleroderma, possibly because, in those years, the evidence was not considered compelling enough. However, nowadays, the judgment might change, and new initiatives might be more successful. In 2016, the guideline (S2k, AWMF) of the Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin and the Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin on silicosis including Coal Worker's Pneumoconiosis stated: "…*the medical scientific knowledge it is unclear [on] whether certain disorders of the rheumatic group such as scleroderma or Caplan syndrome, which are sometimes associated with silicosis (or coal workers' pneumoconiosis), belong in toto to the occupational disease number 4101 (silicosis)*" [132]. On the other side, advisory boards, such as the UK Industrial Injuries Advisory Council, stated seven years ago that "…*crystalline silica is likely to be a cause of connective tissue disease in some circumstances*" [133]. More recently, a Swiss paper described the cases of four patients suffering from scleroderma who applied to their accident insurance companies for compensation, given their exposure and the data in the literature. The Swiss National Accident Insurance Fund recognized two of them as occupational diseases. To call for the attention of general practitioners and rheumatologists, the authors designed a short questionnaire meant to help them identify scleroderma patients likely to have an occupational disease [134]. These questions addressed a few occupations considered relevant for silica exposure.

This systematic review suggests that the diagnosis of rheumatoid arthritis, scleroderma or SLE in a patient, especially if male and retired or close to retirement age, should induce the suspicion of an occupational origin. Occupational information should always be part of an accurate anamnesis; it is of utmost relevance to detect current or past exposure to silica as a possible contributing factor and alert the patient of his/her right to claim compensation. For an occupational origin to be acknowledged and compensation claim considered, several conditions apply, assuming their association with a significant 50% excess risk for the condition (rheumatoid arthritis or scleroderma, respectively).

1. The risk of scleroderma and SLE seems to increase by about 50% after 6 or more years from the onset of silica exposure; an approximately similar excess risk of rheumatoid arthritis has been reported for exposures lasting 2 or more years [23,24];
2. An approximate 50% excess risk for rheumatoid arthritis, scleroderma, and SLE has been related to an average exposure to silica above 2 mg/m^3 [24], which would be 20 times higher than the 0.1 mg/m^3 threshold adopted by the European Community in 2017 [135] and 40 times higher than the permissible exposure standard according to the U.S. Occupational Safety and Health Administration [136]. Ideally, exposure information should rely on historical workplace measurements; alternatively, expert semi-quantitative exposure assessments may be accepted to achieve a reasonable estimate of the average exposure level for each specific case;
3. Latency, i.e., the years between silica exposure onset and the diagnosis of rheumatoid arthritis or scleroderma had been suggested to range 1–38 years [32], too imprecise to define an acceptable threshold;
4. Previous radiological evidence of silicosis has been associated with a 12-fold excess risk of rheumatoid arthritis in a prospective cohort study [23]; therefore, according to the current status of knowledge, it should be sufficient to establish a causal relationship based on the job title even in the absence of any exposure assessment.

In conclusion, the current status of knowledge justifies asserting that it is time for the Health Insurance and Compensation Agencies worldwide to consider compensating selected cases of rheumatoid arthritis, scleroderma and systemic lupus erythematosus as occupational diseases.

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