Original Article

Risk factors for the development of systemic sclerosis: a systematic review of the literature

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Abstract

Objectives. Although numerous studies have investigated the roles of various genetic, epigenetic and environmental factors that may impact its aetiology, SSc is still regarded as an idiopathic disease. Given that there is significant heterogeneity in what has been proposed to influence the development of SSc, this systematic review was conducted to assess the impacts of different factors on the aetiology of scleroderma.

Methods. The search was performed in the PubMed, CINAHL and SCOPUS databases on 17 May 2017. Any study that made explicit reference to scleroderma or SSc that had information about the risk factors or epidemiology of the disease was included. The extracted outcome variables were prevalence, gender preponderance, geographical distribution, family history and various proposed environmental risk factors.

Results. One thousand five hundred and seventy-four articles were screened for eligibility. Thirty-four articles were eligible for the systematic literature review.

Conclusion. Age between 45 and 64 years, female sex, positive family history and exposure to silica were found to be risk factors. There were conflicting findings regarding the impact of exposure to organic solvents and microchimerism. No relationship between infectious agents, alcohol consumption or cigarette smoking and the development of SSc was identified.

Key words: scleroderma, systemic sclerosis, risk factors, epidemiology

Key messages

- Middle age, female sex, positive family history and exposure to silica are risk factors for scleroderma.
- Infectious agents, alcohol and cigarette smoking are not risk factors for scleroderma development.

Introduction

Scleroderma, or SSc, refers to a heterogeneous group of autoimmune fibrosing disorders that are chronic, progressive and can lead to fatal complications [1].

The term scleroderma was first used in 1836 by Giovambattista Fantonetti, who published a case study about a 30-year-old woman with the condition in his journal Effemeridi della Scienze Mediche [2]. Fantonetti derived the term from the Greek words skleros and derma, which respectively translate to hard and skin [3].

The epidemiology of SSc has provided some insights into possible causes of the disease. SSc is a rare disease, which suggests that the genetic and environmental factors that predispose to it are also rare [4]. There is marked geographical variation in the prevalence of SSc, ranging from 7 to 658 per million [5–8]. Although this is likely to be attributable, in part, to discrepancies in disease ascertainment, it might indicate that there are...
environmental exposures that predispose to SSc in certain parts of the world [9]. Studies agree on a 7:1 female preponderance, and the onset in most patients is between the ages of 30 and 50 years, which suggests that hormonal factors, pregnancy and age-related influences might play a role [9–13]. Paradoxically, there is a 13- to 19-fold increase in the risk of developing SSc if one has a sibling with the disease, although SSc very rarely runs in families [10–12]. Nonetheless, we still know very little about the underlying causes of SSc and its pathogenesis. The aim of this systematic review is to synthesize what has been discovered regarding the risk factors for the development of SSc, in an attempt to enhance our understanding of the causes of this debilitating disease.

Methods

This study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and is registered at the International Prospective Register of Systematic Reviews [14, 15]. The registration number for this review on the International Prospective Register of Systematic Reviews website is CRD42017067304, and a published protocol for this study can be found there.

Eligibility criteria

In order to be included in this systematic review, the articles had to be studies written in English that involved humans and made explicit reference to scleroderma or SSc. There was no restriction on publication date or study type. Articles were excluded if they used the same data published in another study, in order to reduce the effect of publication bias. The studies had to examine adult-onset scleroderma, rather than juvenile scleroderma (which is a distinct entity from SSc and may have a different aetiology). Articles were excluded if they focused on the proposed effects of silicone breast implants on SSc aetiology, because many studies have found no relationship [4, 6, 7, 13, 16–18].

Search strategy

The systematic search was done on 17 May 2017, using the following databases: PubMed, CINAHL and SCOPUS. The search strategy for PubMed was constructed by the first author, and was as follows: (((risk factors OR risk factor OR risk OR probability OR epidemiol* OR aetiolog* OR etiolog*)) AND (SSc OR scleroderma)) AND (develop*). The search strategy was modified to fit CINAHL and SCOPUS. Duplicates among the databases were excluded. The titles and abstracts of the articles were then screened independently by two authors (S.A. and A.H.-H.). If the title and/or abstract met the eligibility criteria, full texts of the articles were obtained. Any discrepancies in the selection process between the two authors were resolved by discussion. Three additional studies were identified from reference lists of the included articles [9, 10, 19].

Data collection and data items

The articles included in the systematic review were analysed for risk factors that have been suggested for the subsequent development of SSc; these were: patient demographics; positive family history for SSc; occupational exposures to noxious substances (e.g. silica); exposure to infectious agents; microchimerism, oestrogen and pregnancy-related events; cigarette smoking and alcohol consumption; low birthweight and small-for-gestational age; and vitamin D exposure.

The study data collected from the articles were study type, sample size, methodology, author, country and year of publication.

Risk of bias within studies and quality assessment

The quality of each of the articles was assessed according to their study type. A modified version of the Newcastle–Ottawa Scale was used to assess the quality and risk of bias within the case–control and cohort studies [20]. The Newcastle–Ottawa Scale grades articles according to their case selection, comparability and ascertainment of exposure. For systematic reviews and meta-analyses, a standardized quality assessment scale constructed by the National Heart, Lung and Blood Institute was used, and for narrative reviews, a scale proposed by La Torre et al. [21, 22], called the International Narrative Systematic Assessment score, was used.

Results

Study selection

The search retrieved a total of 2347 results. Seven hundred and seventy duplicates were identified; therefore, 1577 titles were screened. Of these articles, 1268 were excluded because of an irrelevant title, and a further 254 were rejected when the abstract was deemed irrelevant. Fifty-five articles underwent full-text review, which included 5 meta-analyses, 2 systematic reviews, 27 narrative reviews, 15 case-control studies, 3 cohort studies and 3 case reports. Three articles were excluded because they had an inappropriate study design [23–25]. A further eight were excluded because they were not written in English [26–33]. Four articles were excluded because of their focus on the proposed effects of silicone breast implants on SSc aetiology [7, 16, 34, 35]. Another two articles were excluded because they used the data of another study [19, 36]. One article was excluded because it did not make specific reference to SSc [37]. Finally, three articles were excluded because they did not focus on risk factors that lead to the development of SSc [38–41]. A total of 34 articles were finally included in the systematic review [4–6, 8–10, 12, 13, 17, 18, 41–64]. These are outlined in the PRISMA flow diagram shown in Fig. 1. Upon analysis of the included
Risk factors for the development of scleroderma

A summary of the findings for risk factors for SSc derived from the studies is shown in Table 2.

Female sex

Female sex as a risk factor for SSc was assessed in seven of the studies, all of which made note of the marked female preponderance, with female: male prevalence ratios ranging from 3:1 to 8:1 [4, 8, 9, 12, 13, 53].

Age

Patient age was investigated as a risk factor in four of the studies [5, 8, 13, 47]. The common finding between all of the studies was that the risk of SSc peaks between the ages of 45 and 64 years [9, 10, 12].

Geographical and ethnic group distribution

Nine of the studies examined the effects of geographical location and ethnicity [5, 8–10, 12, 13, 47, 49, 52].
| Author, year and country | Type of study and methods | Risk factor(s) examined and ascertainment of exposure | Outcomes |
|--------------------------|---------------------------|------------------------------------------------------|----------|
| Bilgin et al. 2015 Turkey [44] | Case–control (April 2009–March 2012). 30 SSc patients who were admitted to the Konya Training and Research Hospital vs 30 age- and sex-matched controls | Exposure to infectious agents. ELISAs used to detect antibodies against various bacteria and viruses in subjects’ sera | A higher prevalence of infectious agents was found in the SSc patients than in the healthy controls (e.g. 73.3% of the SSc patients had *Helicobacter pylori* antibodies vs 46.6% in the control group) |
| Burns et al. 1996 USA [17] | Case–control (1985–1991). 274 female SSc cases in Michigan and 1184 female population-based controls matched by race, age and geographical region | Exposure to silica. Telephone interview | No significant effect found among those who worked with or around silica (adjusted OR: 1.5; 95% CI: 0.76, 2.93) |
| Chaudhary et al. 2011 USA [46] | Case–control (1998–2009). 621 SSc patients enrolled in the GENISOS or Scleroderma Family Register Studies were matched 2:1 by age, sex, ethnicity and state of residence to controls | Cigarette smoking. Smoking history was ascertained via chart review of the BRFSS and via telephone interview | Cigarette smoking was not found to be a risk factor for SSc (I² = 0.842; OR: 1.020; 95% CI: 0.839, 1.240). |
| Cockrill et al. 2010 USA [48] | Case–control (case–sibling design) (1998–2009). 987 SSc patients enrolled in the GENISOS or Scleroderma Family Register Studies were matched with their unaffected sibling controls (n = 3088) | Increasing birth order, gravidity and parity. Data were obtained from the Scleroderma Family Registry and DNA Repository | Risk of SSc increased with increasing birth order (OR: 1.25, 95% CI: 1.06, 1.50 for birth order 2–5; OR: 2.22, 95% CI: 1.57, 3.15 for birth order 6–9; and OR: 3.53, 95% CI: 1.68, 7.45 for birth order 10–15). History of one or more pregnancies was found to be a risk factor for SSc (OR: 2.8). History of one or more pregnancy losses without any live births had the strongest association with SSc (OR: 9.56, 95% CI: 2.12, 43.15). |
| Donzelli et al. 2015 Italy [50] | Case–control (June 2012–November 2013). 332 SSc cases were identified from the rheumatological outpatient clinics of four Italian hospitals. These cases were matched by age and sex to 243 controls from the surgical outpatient clinic of a hospital in Florence | Low birth weight and small-for-gestational age. A questionnaire and an interview were used to collect self-reported perinatal information on the subjects | Low birth weight increases risk of SSc (OR: 2.59; 95% CI: 1.39, 5.05) Small-for-gestational age increases risk of SSc (OR: 3.93; 95% CI: 1.92, 8.07) |
| Garabrant et al. 2003 USA [51] | Case–control (1980–1992). 660 female SSc cases were identified from numerous databases and mailing lists in Michigan and Ohio. These were matched to 2227 female controls, who were chosen by random digit dialling telephone sampling | Exposure to solvents. Subjects were interviewed by telephone. An expert then verified the exposures with a retrospective exposure assessment | Paint thinners and removers were associated with SSc (OR: 2.0, 95% CI: 1.5, 2.6) Other petroleum distillates and specific solvents (e.g. trichloroethylene) were not significantly associated with SSc |
| Kütting et al. 2006 Germany [54] | Case–control. 109 SSc patients who were part of a SSc support group were matched to 66 MS patients who were part of a MS support group | Exposure to solvents. Subjects were sent a questionnaire and asked to return it anonymously | A non-significant association between occupational exposure to solvents and risk of SSc was found for the male subgroup (OR: 4.794; 95% CI: 0.459, 69.901). No such association found for the other subgroups Significant associations with SSc were found for palladium, cadmium, zinc, antimony, mercury and molybdenum |
| Marie et al. 2017 France [55] | Case–control (2005–2008). 100 SSc cases who were seen in three French medical centres were matched by age, sex and smoking habit to 300 controls | Exposure to heavy metals. Subjects underwent detection of heavy metal traces in their hair samples, using ICP-MS | |

(continued)
TABLE 1 Continued

| Author, year and country | Type of study and methods | Risk factor(s) examined and ascertainment of exposure | Outcomes |
|--------------------------|---------------------------|-----------------------------------------------------|----------|
| Marie et al. 2014 France [56] | Case–control (2005–2008). 100 SSc cases who were seen in three French medical centres were matched by age, sex and smoking habit to 300 controls | Exposure to silica and solvents. Subjects were interviewed using a questionnaire, then a committee retrospectively evaluated exposure | Association found for silica (OR: 5.32; 95% CI: 2.25, 13.09) and for some specific solvents, but not for ‘any type of solvent’ (OR: 1.59; 95% CI: 0.93, 2.67) |
| Nietert et al. 1999 USA [60] | Case–control (March 1995–February 1997). 178 SSc cases diagnosed at the Medical University of South Carolina and 200 controls with musculoskeletal disorders | Exposure to solvents. Questionnaire regarding occupation and hobbies, and ELISA of blood samples for Scl70 detection | Overall participation in SOH was not associated with SSc. Odds of having both SOH and occupational exposure were much greater among those positive for Scl70 compared with controls (OR: 5.8; 95% CI: 1.9, 17.7) |
| Pisa et al. 2001 Italy [61] | Case–control (January 1997–June 1999). 46 female SSc cases diagnosed at an Italian hospital were frequency matched to 153 female controls with orthopaedic disorders | Gravidity and parity. Interview and questionnaire | Parous women had reduced risk of SSc (OR: 0.3; 95% CI: 0.1, 0.8). The risk decreased with increasing number of children. Abortive pregnancies were inversely related to SSc risk (OR: 0.5; 95% CI: 0.2, 1.5) |
| Roberts-Thomson et al. 2006 Australia [9] | Case–control (1993–2002). 353 cases and controls obtained from the Australian Bureau of Statistics consensus | Sex, family history, geographical distribution, ethnicity | Female: male ratio approximated 5:1. Family history was the strongest risk factor (OR: 14.3; 95% CI: 5.9, 34.5). 2.5-fold increased risk for subjects born in continental Europe. Ethnicity did not seem to be a risk factor |
| Russo et al. 2014 Australia [63] | Case–control (1993–2013). 387 SSc cases enrolled in the South Australian Scleroderma Register and 457 controls who were either patients or employees of the authors’ hospitals | Increasing birth order, gravidity and parity. Questionnaire | No significant relationship was found for either birth order or family size with SSc. SSc patients were more likely to be multiparous than controls (OR = 1.8; 95% CI: 1.1, 2.98) |
| Şahin et al. 2013 Turkey [64] | Case–control. 80 female SSc patients and 40 healthy female controls | Microchimerism and parity. Questionnaire regarding subjects’ pregnancy history and PCR of peripheral blood samples to detect microchimerism | SSc was more prevalent in women who had given birth and even more common in those who had male children (P < 0.05). Microchimerism was more common in SSc group than controls (P = 0.180) |
| Aryal et al. 2001 USA [42] | Systematic review and meta-analysis of eight articles published between 1989 and 1998 | Exposure to solvents. Synthesized the findings of the eight included studies | Organic solvents were found to be a risk factor for SSc (RR: 2.91; 95% CI: 1.60, 4.96). Trichloroethylene exposure increases risk of SSc (OR: 2.07; 95% CI: 1.55, 2.78). RR was higher in men (OR: 5.28; 95% CI: 3.46, 8.05) than women (OR: 1.62; 95% CI: 1.34, 1.96). Trichloroethylene exposure increases risk of SSc (OR: 2.07; 95% CI: 1.34, 3.17) |
| Barragán-Martínez et al. 2012 Colombia [43] | Systematic review and meta-analysis of 33 articles published between 1982 and 2011 | Exposure to solvents. Synthesized the findings of eight of the included studies Exposure to silica. Synthesized the findings of the 16 included studies | Significant heterogeneity was detected (P² = 97.2%; P < 0.01). CERR = 3.20 (95% CI: 1.89, 5.43). CERR for females = 1.03 (95% CI: 0.74, 1.44). CERR for males = 3.02 (95% CI: 1.24, 7.35) |
| McCormic et al. 2010 USA [58] | Systematic review and meta-analysis of 16 articles published between 1967 and 2007 | Exposure to solvents. Synthesized the findings of seven of the included studies | Organic solvents increase risk of SSc (OR: 2.07; 95% CI: 1.55, 2.78). RR was higher in men (OR: 5.28; 95% CI: 3.46, 8.05) than women (OR: 1.62; 95% CI: 1.34, 1.96). Trichloroethylene exposure increases risk of SSc (OR: 2.07; 95% CI: 1.34, 3.17) |
| Zhao et al. 2016 China [5] | Systematic review and meta-analysis of 14 case–control studies published between 1989 and 2014 | Exposure to solvents | Four studies out of seven detected lower levels of vitamin D in SSc patients than controls (46–84 vs 40%) |
| Antico et al. 2012 Italy [41] | Systematic review of 219 articles published between 1973 and 2011 | Lack of vitamin D. Synthesized the findings of seven of the included studies | (continued) |
| Author, year and country | Type of study and methods | Risk factor(s) examined and ascertainment of exposure | Outcomes |
|-------------------------|--------------------------|------------------------------------------------------|----------|
| Radić et al. 2010 Croatia [62] | Systematic review of 52 articles published between 1984 and 2008 | Helicobacter pylori infection | Supports hypothesis of H. pylori infection being a cofactor in SSc aetiology |
| Allanore et al. 2015 USA [8] | Narrative review of 208 articles published between 1980 and 2015 | Geographical distribution, family history, smoking, alcohol, silica, vinyl chloride, solvents, infectious agents | SSc is more common in southern Europe, the USA and Australia than the UK and Asia. RR of first-degree relatives = 13. Smoking and alcohol not associated. Silica, vinyl chloride, organic solvents and infectious agents "might be involved" |
| Brasington et al. 1991 USA [45] | Narrative review of 15 articles published between 1965 and 1989 | Solvents | Exposure to organic solvents is a risk factor for SSc |
| Chen et al. 2003 Australia [47] | Narrative review of 80 articles published between 1971 and 2001 | Age, family history, silica, solvents, microchimerism | SSc onset is most common between ages of 30–50 years. Positive family history is the strongest risk factor for SSc (RR = 10–16). Silica and organic solvents are a risk factor for SSc. Microchimerism may be only one part in a multifactorial pathogenesis of SSc |
| De Martinis et al. 2016 Italy [49] | Narrative review of 93 articles published between 1957 and 2015 | Geographical distribution, silica, solvents, infectious agents, smoking | SSc is more common in southern Europe, the USA and Australia than the UK. Current evidence supports silica as a risk factor, is ambiguous regarding organic solvents and infectious agents, and does not support smoking as a risk factor |
| Dospinescu et al. 2013 UK [6] | Narrative review of 38 articles published between 1914 and 2012 | Silica, solvents, smoking | Current evidence suggests silica is a risk factor for SSc, solvents may or may not be a risk factor, and smoking is not a risk factor |
| Gaubitz 2006 Germany [52] | Narrative review of 12 articles published between 1988 and 2003 | Geographical distribution, silica, solvents, vinyl chloride | SSc is more common in the USA and Australia than the UK. Silica, organic solvents and vinyl chloride significantly increase risk of SSc |
| Hamamdzic et al. 2002 USA [53] | Narrative review of 34 articles published between 1984 and 2001 | Infectious agents, microchimerism | Development of SSc is unlikely to depend exclusively on an infectious agent, but rather as a result of the interactions between the infectious agent and a cascade of host-specific factors and events. Microchimeric cells are more common in women with SSc than in healthy controls |
| Marie et al. 2015 France [18] | Narrative review of 121 articles published between 1914 and 2015 | Silica, solvents, smoking, infectious agents, vinyl chlorides, epoxy resins | There is a marked correlation between SSc onset and exposure to silica and various organic solvents. Insufficient data to suggest that infections, smoking, physical agents, vinyl chlorides and epoxy resins play a causative role in the development of SSc |
| Mayes 1996 USA [12] | Narrative review of 56 articles published between 1960 and 1996 | Sex, geographical distribution, ethnicity, family history | SSc occurs much more frequently in women than in men. SSc is five times more common in the USA than in Britain and Japan. African-American (continued) |
Seven of these articles discovered a higher prevalence in Australia and North America compared with Continental Europe, the UK and Japan [5, 8, 10, 12, 13, 49, 52]. SSc was found to be more prevalent in African-Americans than Caucasian Americans in six of the studies [8, 12, 13, 36, 49, 52]. One study, on the contrary, did not find an association with ethnicity [9]. A north–south gradient in Europe was reported in two of the studies, with the incidence being lower in northern Europe [10, 49].

Positive family history
Seven of the studies discussed the impact of a positive family history on SSc susceptibility [4, 8–10, 12, 13, 47]. All of these studies reported a positive family history as a risk factor for SSc, and four of them suggested that it is the strongest risk factor for development of SSc, with odds ratios (ORs) varying between 10 and 16 [8–10, 47]. In contrast, the other three studies argued that it is unlikely that genetic factors are a major cause of SSc [4, 12, 13].

| Author, year and country | Type of study and methods | Risk factor(s) examined and ascertainment of exposure | Outcomes |
|--------------------------|--------------------------|-------------------------------------------------------|----------|
| Mayes 1999 USA [57]      | Narrative review of 65 articles published between 1967 and 1998 | Oestrogens, silica, solvents | Oestrogen replacement therapy increases risk (1.5- to 3-fold), but COCP does not. Silica exposure does not explain most cases of SSc in men and does not play a significant role in women. Role of solvent exposure is unclear |
| Mora 2009 Argentina [59] | Narrative review of 154 articles published between 1949 and 2007 | Silica, vinyl chloride, solvents, infectious agents, microchimerism, oestrogens | Silica exposure is a risk factor. Ambiguous regarding vinyl chloride and organic solvents as risk factors. SSc is associated with H. pylori and viral infection. Microchimerism may explain female preponderance. Oestrogen replacement therapy increases risk, but COCP does not |
| Nikpour et al. 2010 Australia [10] | Narrative review of 100 articles published between 1957 and 2010 | Geographical distribution, ethnicity, family history, sex, solvents, silica | SSc is more common in the USA and Australia than Japan and Europe. More common in black than white Americans. 13- to 14-fold increased risk if first-degree relative with SSc. 7:1 female preponderance. Solvents and silica are a risk factor for SSc |
| Silman 1991 UK [13]     | Narrative review of 112 articles published between 1914 and 1991 | Geographical distribution, genetics, silica, solvents, smoking, alcohol | Prevalence in Japan is much lower than in Western countries. Unlikely that genetic factors are a major cause. Silica exposure is a risk factor. Numerous organic solvents have been implicated. Smoking is not a risk factor, but alcohol is |
| Silman et al. 1994 UK [4] | Narrative review of 39 articles published between 1985 and 1994 | Family history, occupational exposures, infectious agents | Multiple affected kinships are rare. Silica and organic solvents may lead to sporadic cases, but the attributable risk is low. There is very little evidence for a viral link to SSc |
Exposure to organic solvents

Occupational exposure to organic solvents was investigated in 18 of the studies, with significantly variable results [5, 6, 8, 10, 13, 18, 42, 43, 45, 47, 49, 51, 52, 54, 56, 57, 59, 60]. Eleven of these articles found a significant correlation between exposure to organic solvents and SSc, with ORs ranging between 2.07 and 2.91 [5, 10, 13, 18, 42, 43, 47, 49, 52, 56, 60]. Conversely, two other studies found that exposure confers a significantly increased risk of SSc to men, but not to women [54, 59]. A further three studies were inconclusive [6, 45, 57]. One article could only find a relationship between paint thinners and removers with SSc, but could not find a significant association between other specified solvents and SSc [50]. Finally, the remaining article argued against any such risk [8].

Exposure to silica

Exposure to silica as a risk factor for SSc was examined in 14 of the included articles and was reported to be a significant risk factor in nine of them (including one meta-analysis), with ORs ranging between 2.07 and 2.91 [5, 10, 13, 18, 42, 43, 47, 49, 52, 56, 60]. Conversely, two other studies found that exposure confers a significantly increased risk of SSc to men, but not to women [54, 59]. A further three studies were inconclusive [6, 45, 57]. One article could only find a relationship between paint thinners and removers with SSc, but could not find a significant association between other specified solvents and SSc [50]. Finally, the remaining article argued against any such risk [8].

Infections

Exposure to infections as a risk factor was studied in eight of the included articles, again with considerable heterogeneity [4, 8, 10, 13, 18, 44, 53, 59, 62]. Four of the articles reported a positive correlation between infectious agents with SSc [8, 10, 13, 18]. In contrast, two of the studies reported that there have been conflicting results in the literature regarding infections and SSc but concluded that their involvement in the disease cannot be ruled out [53]. The final three studies stated that there is insufficient evidence in the literature to implicate either bacterial or viral infection as a risk factor for SSc [4, 18, 49].

Insufficient vitamin D exposure

Two of the included studies investigated the effects of hypovitaminosis D on SSc, and they both concurred that vitamin D deficiency can be a risk factor for SSc [41, 49].

Cigarette smoking and alcohol consumption

All of the six studies that investigated smoking and alcohol consumption as a risk factor for SSc found neither of them to be significant risk factors [6, 8, 13, 18, 46, 49].

Exposure to heavy metals

Exposure to heavy metals was examined in one study, which found a significant correlation between SSc and exposure to a number of heavy metals, including palladium, cadmium, zinc and antimony [55].

Microchimerism and pregnancy-related events

Microchimerism refers to the persistence of the retained cells from the fetus of a previous pregnancy in a mother’s peripheral bloodstream. The possible effects of microchimerism as a risk factor for SSc were investigated in eight of the articles included in this review [12, 47, 48, 53, 59, 61, 63, 64]. Five of these articles reported microchimerism as being more common in SSc patients than in controls and found a positive relationship between SSc and a history of pregnancy (especially a history of having had a son) [47, 48, 53, 59, 64]. The other three studies failed to show a relationship and argued against microchimerism as a risk factor [12, 61, 63].

Low birthweight

One of the included studies examined low birthweight as a risk factor and found a statistically significant

Table 2 Summary finding of risk factors for the development of SSc

| Risk factor                      | Number of studies | Regarded as a risk factor (based on available evidence) | Level of evidence (based on heterogeneity and quality assessment scale of the included studies) |
|----------------------------------|-------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Female sex                       | 7                 | Yes                                                      | High                                                                                       |
| Age between 45 and 64 years      | 4                 | Yes                                                      | High                                                                                       |
| Geographical distribution and ethnicity | 9                | Yes                                                      | Moderate                                                                                  |
| Positive family history          | 7                 | Yes                                                      | High                                                                                       |
| Exposure to organic solvents     | 18                | Yes                                                      | Moderate                                                                                  |
| Exposure to silica               | 14                | Yes                                                      | Moderate                                                                                  |
| Infections                       | 8                 | Yes                                                      | Moderate                                                                                  |
| Insufficient vitamin D exposure  | 2                 | Uncertain                                                | Low                                                                                       |
| Smoking and alcohol              | 6                 | No                                                       | High                                                                                       |
| Exposure to heavy metals         | 1                 | Yes                                                      | Moderate                                                                                  |
| Exposure to physical agents      | 1                 | No                                                       | Moderate                                                                                  |
| Microchimerism                   | 8                 | Uncertain                                                | Moderate                                                                                  |
| Low birthweight                  | 1                 | Yes                                                      | Moderate                                                                                  |
correlation between SSc and low birthweight (OR: 3.93; 95% CI: 1.92–8.07), and between SSc and small-for-
gestational age (OR: 2.58; 95% CI: 1.28–5.19) [50].

Table 2 summarizes these findings.

Discussion

This review found complete concordance with the fact
that SSc is primarily a disease of middle-aged women,
as expected. Likewise, there was strong concordance
regarding the geographical distribution of patients with
SSc. In contrast, the finding of a north–south gradient
across Europe, with SSc being less frequent in northern
Europe, is out of keeping with the findings of an Italian
systematic review by Antico et al. [10, 41, 49], which
found that patients with SSc have lower vitamin D levels
than healthy controls, in percentages varying from 46 to
84%. However, this finding was based on a modest to-
tal of 313 subjects, whereas the epidemiological studies
that have noted the higher frequency of SSc in southern
Europe have been based on significantly larger, better-
powered registries. Therefore, even if vitamin D defi-
ciency is a risk factor for SSc, it seems that there must
be other environmental exposures in southern Europe
that predispose to SSc that can still contribute to the
development of SSc in patients with normal vitamin D
levels.

A positive family history of SSc has repeatedly been
reported as the strongest risk factor for the development
of SSc, but in spite of this, numerous studies have
noted that monozygotic twins with SSc are very rare
and that 98% of SSc patients do not have another af-
fected family member of any degree of blood relation
[9, 12, 47]. The logical explanation for this would be that
there is a modest genetic predisposition for SSc and
that the environmental exposures necessary for the de-
velopment of SSc in a predisposed person are uncom-
mon. Therefore, although the brother of a patient with
SSc may be at a 14-fold increased risk of developing
SSc throughout his lifetime, the absolute risk of him de-
veloping SSc is low, owing to the rarity of the putative
environmental exposures necessary for SSc to occur
[10].

Perhaps the most contentious issue regarding envi-
rmental risk factors for SSc is the exposure to organic
solvents. This review included three meta-analyses that
examined organic solvents as a risk factor for SSc, all of
which found a significant correlation between SSc and
exposure to organic solvents, with combined OR values
ranging from 2.07 to 2.91 [5, 42, 43]. Although these
results appear compelling, there is the possibility of a
significant publication bias, either owing to researchers
not submitting negative results or owing to journals de-
clining to publish the findings of studies that have not
found organic solvents to be a significant risk factor for
SSc. Furthermore, all of the four case–control studies in-
cluded in this review that reported a significant correla-
tion between SSc and organic exposure were ret-
rospectively based on self-reported exposure and were
therefore subject to significant recall bias [51, 54, 56,
60]. Finally, as noted by Dospinescu et al. [6], exposure
to organic solvents has usually been ascertained on the
basis of the subjects’ occupations, and it is likely that
these subjects (e.g. miners) had concomitant, confound-
ing exposure to other environmental agents. Therefore,
although the consensus in the literature favours organic
solvents as being a significant risk factor for SSc, the
evidence for this is still arguably dubious.

Of all of the environmental exposures that have been
investigated as risk factors for SSc, occupational ex-
sposure to silica appears to be the most convincing. A well-
designed meta-analysis by McCormic et al. [58] found
a significant relationship between occupational silica ex-
posure and SSc, with a combined estimator or relative
risk of 3.20 (95% CI: 1.24–7.35). In contrast, a large
case–control study by Burns et al. [17] did not detect
any effect of occupational exposure to silica on the risk
of SSc, but this study only included female subjects,
who are less likely to experience occupational expos-
ures to silica than men (e.g. as in abrasive grinding,
mining and sandblasting). This is in keeping with the
finding of Mora et al. [59], who argued that occupa-
tional exposure to silica significantly increases the risk of SSc
in men, but not in women, primarily because the expo-
sure to silica of the male cohort is far greater.

Although the theory of infection leading to molecular
mimicry and causing autoimmune disease is biologically
plausible, there is currently insufficient evidence to sup-
port the notion of infection being a significant risk factor
for SSc. In a case–control study involving a modest total
of 30 patients with SSc, Bilgin et al. [44] found that
a higher proportion of SSc patients had antibodies against
Helicobacter pylori, CNV, EBV and parvovirus B19.
However, that study did not account for the impact of
other environmental factors on the development of SSc
(i.e. did not adjust the results with multivariate logistic
regression), which limits the validity of the conclusions.
Owing to the poor quality of this evidence, infections are
not regarded as a risk factor for SSc [4, 18]. Likewise,
there is insufficient evidence for cigarette smoking as a
risk factor for the development of SSc, although it might
exacerbate the severity and prognosis, once the disease
process has begun [6, 46, 49].

Microchimerism as a risk factor for SSc is an interest-
ing theory, which stemmed from the observation of an
obvious female preponderance, with females being af-
fected preferentially in the post-childbearing years [47].
It has since been discovered that microchimeric cells
are more commonly detected in women with SSc than
in healthy controls [47, 53, 59]. These observations moti-
vated many of the studies included in this review, which
yielded widely conflicting results. Firstly, Cockrill et al.
[48] found, in their highly powered case–control study
involving 987 patients with SSc and 3088 sibling con-
trols, that a history of pregnancy reduces the risk of SSc by an OR of 2.8. In direct
contrast to this, Pisa et al. [61], in their case–control
study, found that a history of pregnancy reduces the
risk of SSc (OR: 0.3; 95% CI: 0.1–0.8). It would seem that microchimerism is only one of a multitude of factors that have been implicated in the pathogenesis of SSc but are yet to be proven aetiological factors. This is evidenced by the observation that microchimerism occurs in many healthy, normal women, and SSc often occurs in nulliparous women [47, 61].

Although the articles that examined exposure to heavy metals and low birthweight in this review were strong studies, there are currently insufficient data in the literature to confirm whether or not these factors predispose to the development of SSc [18, 50, 55]. Further research in these areas would be valuable to determine the role of these agents in SSc pathogenesis.

Ultimately, ascertaining the risk factors that predispose to SSc is an ongoing dilemma for three reasons. Firstly, SSc is a very rare disease, making it difficult to obtain cohorts that are adequately powered to provide meaningful data. Secondly, the majority of environmental exposures that are currently under investigation are often experienced concomitantly, and therefore it may be impossible to attribute the development of SSc to one exposure alone. Thirdly, in order to implicate an exposure in SSc aetiology fully, prospective studies are required, because retrospective studies are subject to significant recall bias. The feasibility of such studies is doubtful, because the likelihood of a subject developing SSc as a result of being exposed to a given agent is extremely low, and there are obvious ethical implications involved with risking the development of such a debilitating disease in a subject. Although we have discovered that occupational exposure to silica is a significant risk factor in SSc, in addition to a number of aforementioned patient demographics, the absolute and attributable risks of these factors to SSc aetiology are clearly low, because the vast majority of individuals with these risk factors do not develop SSc. Unfortunately, performing a meta-analysis for the various risk factors for SSc was not possible for the present review, owing to there being excess heterogeneity among the literature. Therefore, as noted numerous times by Roberts-Thomson et al. [9, 19], SSc is likely to result from a number of stochastic events that are impossible to identify, thus SSc may continue to be seen as an idiopathic disease.

Conclusion

In conclusion, this review found age between 45 and 64 years, female sex, living in the USA and Australia, positive family history and occupational exposure to silica to be significant risk factors for the development of SSc. There were conflicting findings regarding the impact of exposure of organic solvents and microchimerism on the development of SSc. There are currently insufficient data to implicate infectious agents as a risk factor. Alcohol consumption and cigarette smoking were not found to be risk factors. Given that we currently have only empirical treatment for SSc, the possible prevention of this disease is of the utmost importance. The results of this review suggest that industries involving exposure to silica should ensure that their staff use protective measures and have regular health checks to limit the possibility of their occupational exposure leading to the development of SSc. Further research is required to ascertain the role of organic solvents, microchimerism and infectious agents as risk factors for SSc.

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Supplementary data

Supplementary data are available at Rheumatology online.

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