Crystalline silica exposure in patients with rheumatoid arthritis and systemic sclerosis: a nationwide cross-sectional survey

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Title page

TITLE of the article

Occupational exposure to crystalline silica in patients with systemic sclerosis and rheumatoid arthritis. Findings from a thorough questionnaire in a nationwide cross-sectional study

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- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abstract (250 words, divided into Objectives, Methods, Results and Conclusion): **242 words**

Objectives

Develop and validate a thorough exposure questionnaire to comprehensively explore crystalline silica (SiO_2) exposure in the general population (gender-specific, occupational and non-occupational) and in patients with autoimmune diseases (Rheumatoid arthritis (RA), Systemic sclerosis (SSc)).

Methods

Lifetime exposures to SiO_2 in occupational and non-occupational settings were assessed using a thorough exposure questionnaire. The questionnaire was applied to a general population panel (N=2,911) sampled from the French rolling census, and to unselected patients with SSc (N=100) and RA (N=97). Global (GES), occupational (OES) and non-occupational (NOES) exposure scores were assessed in SSc and RA patients, and compared to up to 4 controls from the general population, matched by age group, sex and tobacco consumption.

Results

Patients had higher GES than their matched controls (SSc: p=0.001; RA: p<0.0001) due to higher OES (p<0.0001 for SSc and RA). Men had higher GES than women (SSc: p<0.0001; RA: p=0.002) due to higher OES (p<0.0001 for SSc and RA). The NOES did not differ between men and women.

In SSc patients: Men had higher GES than controls (p<0.0001). Men and women with SSc had higher OES than controls (p<0.0001).

In RA patients: GES and OES were higher in both men (p=0.00521; p<0.0001) and women (p<0.0001; p<0.0001) than in their respective controls. Women had higher NOES than controls (p=0.045).

Conclusion

The lifetime SiO_2 exposure gap between RA and SSc patients and controls was substantially due to occupational exposure. In both diseases, men had higher exposure scores than women.

Clinical trial registration number (for all RCTs): NA

Keywords (up to 10 – please note that the word count refers to individual words, not phrases)

Crystalline silica / Systemic sclerosis / Rheumatoid arthritis / Occupational and non-occupational exposure

Key messages (up to 3, maximum 15 words each)

1 – Patients with SSc and RA had significant lifetime occupational overexposure to SiO_2.

2 – Occupational exposure in men with SSc or RA was higher than in women.

3 – Physicians should carefully assess past silica exposure, which could unlock financial compensation for patients.

References (up to 50): 44

Tables/figures: 5 included in the article

+ 2 Texts, 1 Figure & 2 Tables in Supplementary Material

Word count: 3,885

INTRODUCTION

Crystalline silica (or silicon dioxide, SiO_2), mainly occurring as the polymorphs quartz (the most common in nature and manufacturing processes), cristobalite and tridymite, is one of the most ubiquitous environmental components.

Resulting from exposure to SiO_2, silicosis was initially defined in 1930 at a conference jointly organized by the International Labour Organization and the Transvaal Chamber of Mines, a South African mining-industry employer organization (1,2). Ensuing decades saw the involvement of SiO_2 highlighted in pulmonary alveolar proteinosis and systemic autoimmune diseases such as systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus (SLE), and ANCA-associated vasculitis (AAV) (3–5). The link between RA and SiO_2 has been well documented in large cohorts of construction workers (6). Exposure to SiO_2 may contribute to "decreasing the threshold for the development of autoimmune disease in general", but could also trigger the onset of some clinical manifestations of these diseases (7). The association between SiO_2

and SSc, the rheumatic disease with the highest individual mortality rate, has been continuously reported in several case-control and cohort studies (8,9). Studies conducted since 2000 have strengthened the association of SiO_2 and systemic autoimmune diseases, especially for exposure from cutting, polishing or bevelling new high-silica content materials (10,11), out of the mining sector (12,13).

Large-scale case-control or cohort studies exploring the association between SiO_2 and autoimmunity rarely (if ever) consider non-occupational exposures. The general difficulty of producing a standard measure of "normal" exposure to crystalline silica (14) reflects the lack of standardized questionnaires able to explore SiO_2 exposure as a whole, and to identify the sources of exposure over a lifetime in the general population and in people with autoimmune diseases.

The objective of this study was to develop and validate a thorough exposure questionnaire to comprehensively explore SiO_2 exposure in the general population (gender-specific, occupational and non-occupational). First, we administered the questionnaire to a large representative sample of the French general population (sampled from the general French rolling census). Next, we assessed and compared silica exposure in patients diagnosed with SSc or RA versus the general population.

MATERIAL AND METHODS

Assessment of exposure to mineral dusts

Designing the questionnaire

The Dust Exposure Life-Course Questionnaire (DELCQ) mainly aimed to assess exposure to SiO_2. To reach sufficient sensitivity, we prepared a list of questions based on the inventory of exposure activities made by the Working Group on the Evaluation of Carcinogenic Risks to Humans (15). To develop a thorough inquiry, we supplemented this large list of exposure activities by broadening their spectrum with medical or statistical surveys of the general population (16–18). We added in data from the literature on exposure to SiO_2 and inorganic particles in occupational or environmental settings, including clinical case reports (on clay eating (19), exposure to cat litter dust (20), talcum spreading on abraded skin (21), and air contamination by working clothes as in the case of asbestos (22)), as well as metrological and epidemiological questions on the average silica concentration in ambient air (14).

Drawing on lessons from the sociology of labor (23), we avoided asking people about pre-labelled occupations/"jobs". DELCQ is distinctive in helping respondents designate the actual "activities"

149 they performed in their various occupations. To this end, we phrased matter-of-fact questions that
150 explicitly and precisely referred to products, gestures, equipment, and contexts in which substances
151 were handled, and that used the familiar and/or commercial names of products. The wealth of
152 questions helped maximize the sensitivity of the questionnaire, while their evocative nature
153 maximized its specificity.

154 As far as we know, DELCQ unprecedentedly addresses both occupational *and* non-
155 occupational exposure (in two consecutive modules) over a lifetime.

156 Whereas most questions focused on occupational and non-occupational exposure to silica,
157 some additional ones explored exposure to other inorganic particles. Two questions were about
158 (active and passive) exposure to asbestos at work, and two others probed non-occupational
159 exposure to asbestos, and other mineral, metallic or wood particles (shaking, washing, ironing…
160 dusty working clothes). At the end of each of the two modules, respondents could add any other
161 exposure to silica or other mineral, metallic, wood, leather, diesel or soot particles they might have
162 experienced.

163 *Content of DELCQ, & quantification of exposure*

164 The questionnaire evaluated:

165 1) Sociodemographic and socioeconomic characteristics, highest degree earned, current or
166 latest employment status, and professional skills.

167 2) Health status through: a) the Mini-European Health Module (24) which comprises 3
168 questions on *i)* self-assessed health status (25), *ii)* presence/absence of at least one current chronic
169 disease defined as lasting or likely to come back during 6 months or more, *iii)* functional limitations
170 in daily activities because of health issues; b) specific questions about diseases of interest (silicosis,
171 tuberculosis, emphysema, asthma, chronic obstructive pulmonary disease (COPD), asbestosis or
172 pleural plaques, idiopathic pulmonary fibrosis, lung cancer, sarcoidosis, other respiratory diseases,
173 RA, SSc, SLE, other connective tissue diseases, vasculitis, and any disease that the respondent
174 thought or had been told may be caused/aggravated by exposure to crystalline silica or other
175 inorganic particles; c) the administrative recognition of an occupational disease, or of a long-term
176 chronic disease associated with a special financial status in the French social welfare system; d)
177 medical leaves and hospitalizations (at least one night in the past 12 months); e) lifetime tobacco
178 use (cigarette pack-years); f) height, weight; g) sniffing practices (cocaine or other inhaled drugs,
179 scouring powders); h) drug injection.

180 The questionnaire included 90 questions about occupational exposure and 47 about non-
181 occupational exposure. While they thoroughly explored numerous forms of exposure to SiO_2, the

two modules also sought to quantify the exposure level according to the respondent's self-assessment. For more than 95% of the questions, the respondent had to answer a first screening question exploring an occupational or non-occupational setting *potentially* at risk of exposure to SiO_2. If answered in the affirmative, one or more questions followed to assess whether the respondent had been involved in specific exposure activities in this setting, and if so, the cumulative duration of exposure in his/her life (<1 year; [1;5[years; >= 5 years) and the level of protection (mainly respiratory but also cutaneous and ophtalmological) from dust he/she had used (from (i) never protected or protection always ineffective; to iii) always effectively protected) (**Supplementary Text 1**). A dust exposure score was then calculated based on the duration and the effectiveness of protections against dust (see Suppl. Fig. S2 in (26)). We applied this inquiry approach to most of the situations reviewed, predominantly occupational exposure (48 different occupational scenarios and 18 non-occupational scenarios). Alternatively, the first relevant question could directly focus on a specific exposure activity, without the first filter question about the at-risk setting (**Supplementary Text 2**). Assessing the level of protection was not always relevant, notably in non-occupational contexts. For instance, the use of talcum powder on abraded skin was by definition not associated with cutaneous protection. In such (exceptional) situations, the number of points we added to the dust score was equivalent to that of an exposure without protection.

Our method enabled the calculation of a global exposure score (GES) encompassing all exposures, which could be broken down into an occupational exposure score (OES) and a non-occupational exposure score (NOES) (GES=OES+NOS), or into any specific exposure score.

Throughout the questionnaire, we did not display the possibility to refuse to answer or say "I do not know" at first. Both in the telephone and face-to-face interviews and on tablets, our first proposal only consisted in response items. This ensured a high response rate. If a respondent finally decided to refuse to answer or did not know how to, he/she could get around the question. By proceeding this way, we hardly got missing values. In particular, there were no missing values among the data the exposure scores are based upon.

Fieldwork and questionnaire processing

1 – French general population

Presentation and processing

Panelists were sampled from the general population by the French National Statistical Institute (INSEE) using national rolling census data. They answered the questionnaire in 2014

(ELIPSS-(Longitudinal Online Social Science Survey)-Silice 1(n=825) and in 2016 ELIPSSilice2 (n=2,937) (**Supplementary Figure 1**). The questionnaire was self-administered on tablets. Most of the time, answering the questionnaire took between 35 and 40 minutes. (See **Supplementary Table 1** on response rates).

Exploration of self-declared RA

Given that respondents might confuse self-declared RA with other conditions (e.g. "arthritis" or "osteoarthritis"), for ELIPSSilice2 we revised our questionnaire with the following addition regarding RA: "Did a physician diagnose you with this disease using the term 'rheumatoid arthritis'?". As a result, the statistical analyses including data on self-declared diseases encompassed the 2,739 people who responded to at least ELIPSSilice2 (and potentially to ELIPSSilice1 & 2). We thus sought to eschew results based on false RA positives (27).

2 – Populations of patients from expert centers, diagnosed with systemic autoimmune diseases

Patient populations

SSc patients in the department of Internal Medicine and Clinical Immunology of Rennes University Hospital who met the ACR/EULAR 2013 classification criteria for the disease were consecutively included in the study between 2016 and 2018 (26). RA patients in the department of Rheumatology of Avicenne Teaching Hospital (GHUPSSD, APHP, Bobigny, France) were included in 2016, and all met the 2010 ACR/EULAR classification criteria for RA. For SSc and RA patients, questionnaires were administered by phone or in face-to-face interviews by 4 trained evaluators. The interview usually lasted 45 to 60 minutes. (See **Supplementary Table 1** on response rates and data collection methods). One hundred patients with SSc (median age=63.0 years, IQR=17.0) and 97 patients with RA (median age=60.0 years, IQR=16.0) were included.

Ethics

The databases were declared to the French authorities under the following entry: Comité consultatif sur le traitement de l'information en matière de recherche (CCTIRS) n° 08-015bis and n°12-263bis, Commission Nationale de l'Informatique & des Libertés (CNIL, France), decision DR 2012 525 and decision 1980161v0. All SSc and RA patients gave their informed consent. Local review boards (in Rennes and Bobigny) approved the studies.

Statistical methods

Scores (GES, OES, NOES) are expressed as median (IQR) & mean (+/-SD). Scores obtained by patients diagnosed with RA or SSc were compared to those of matched controls using the Wilcoxon test (level of significance: $p<0.05$). For each patient, we randomly sampled up to 4 controls among ELIPSSilice2 respondents in strata matched by age range, sex and tobacco consumption (number of pack-years). Two situations were considered: 1) *Scenario #1*: controls were selected among people "declaring not to have the disease carried by the matched patient". This meant that controls could have (or have had) *another* chronic condition; 2) *Scenario #2*: controls were selected among people "declaring to have (or have had) *none* of the chronic conditions (i.e. neither the disease of the matched patient, *nor any other* chronic conditions evaluated in the questionnaire)". The data were tabulated with SAS v9.4, R and RStudio 2022.07.0 software.

RESULTS

1 – Exposure scores in the general population

Among the 2,911 panelists who responded to ELIPSSilice1 only, ELIPSSilice2 only, or ELIPSSilice1 & 2, the lifetime prevalence of self-declared SiO_2 exposure (i.e. a strictly positive GES) was 90.7%, with a mean exposure level of 17.97 (SD=20.4), and a median exposure level of 12.0 (IQR=20.0) (**Supplementary Table 2**). The prevalence of exposure in occupational settings (OES>0) was 46.0%, and the prevalence of exposure in non-occupational settings (NOES>0) was 87.9%.

The dust exposure score varied according to the age of the respondent at the time of the questionnaire (**Figure 1**). Among the 2,911 panelists of ELIPSSilice1 & 2, the GES reached a maximum of 21 points for people aged 55-59, and decreased thereafter. The OES decreased after age 65, while NOES showed a slight and gradual decrease after age 60-64.

2 – Case-control comparison of SiO_2 exposure: respondents in the general population *versus* patients diagnosed with systemic diseases

Median GES in SSc and RA patients were 23.0 (IQR=29.0) and 26.0 (IQR=25.0), respectively (**Table 1**). Median OES were 9.5 (IQR=20.0) and 10 (IQR=15.0), and median NOES were 12.0 (IQR=16.5) and 15.0 (IQR=13.0), again in SSc and RA patients respectively, providing

a compared profile of the two diseases in which higher GES in RA appeared to be supported by higher NOES, whereas exposure in occupational contexts would be more specific to SSc. Regardless of the method used to sample matched controls (Scenarios #1 & 2), SSc patients and RA patients had significantly higher GES than the controls. For both diseases, this significant difference stemmed from a significantly higher occupational exposure, whereas non-occupational exposure did not differ between patients and controls.

3 – Relationships between sex and SiO_2 exposure in SSc and RA

Among patients diagnosed with SSc and patients diagnosed with RA, male patients had significantly higher GES than female patients (**Table 2**). This difference stemmed from a significantly higher exposure for male patients in occupational settings. In non-occupational settings, NOES in female and male patients did not differ. The comparison of exposure levels between SSc and RA by sex showed that SSc male patients had higher GES than RA male patients as a result of higher OES, whereas female RA patients had higher GES than SSc female patients by virtue of a higher NOES (**Table 2**). In the general population (ELIPSSilice1 & 2), median GES in women and men were 9.0 (IQR=15.0) and 15.0 (IQR=27.0), respectively (**Table 3**). Median OES were 0.0 (IQR=4.0) and 4.0 (IQR=16.0), and median NOES were 7.0 (IQR=11.0) and 9.0 (IQR=15.0) in both sexes, respectively.

We stratified cases and controls by sex, age, and tobacco use (**Table 4**). Among SSc patients, only men (and not women) had higher GES than their controls. Yet both women and men with SSc had significantly higher OES than their matched controls, while NOES did not differ. GES and OES were significantly higher for both male and female RA patients, compared with their matched controls. NOES were significantly higher only in women with RA versus their matched controls. These results are conservative, as they are drawn from Scenario#1, for which the DELCQ's gap between diagnosed patients and respondents was lower (**Table 1**).

DISCUSSION

This study extensively explored SiO_2 exposure in the French general population and in populations with two autoimmune diseases repeatedly associated with this exposure in the literature. The use of a novel inquiry tool based on social science and statistical skills enabled a thorough assessment of lifetime silica exposure. Importantly, the questionnaire focused on the

actual sources and circumstances of exposure, thereby providing unprecedented accuracy in exposure assessment.

Compared to other analogous inquiry tools (16, 28), this questionnaire is unique in endeavouring to capture occupational *and non-occupational* exposures, also via thorough questioning.

The high prevalence of a history of exposure to silica found in this survey (90.7%) underscores the ubiquity of occupational and non-occupational exposure to one of the most common mineral components of the earth crust, when a sensitive questionnaire is used. The only French statistical survey (SUMER, Medical Follow-Up of Exposure to Occupational Hazards) that has measured it (in 1994, 2003, 2010, 2016-2017) considers only occupational exposure to SiO_2 in the general population, and allows occupational physicians to select "yes" only for workers exposed during the latest working week (29). This lack of systematicity (30) has yielded the excessively low finding that a paltry 1.4% of salaried workers are exposed to silica (16).

Other nationwide studies on SiO_2 exposure (28,31,32) have also solely focused on occupational exposure. The prevalence of SiO_2 exposure in those studies ranged from 17% (in men) (31) to 1.0% (in women) (28), depending on several parameters (e.g. cross-sectional survey *versus* cohort, exposure assessed in current job *versus* all *cursus laboris*, assessment via exposure-job matrices). In the Danish nationwide survey (31), higher exposure levels were associated with older age. The same trend appeared in our work, although respondents over 64 years old reported lower OES than patients aged 45-64. This could be attributable to the retrospective nature of the evaluation, introducing memory biases (analogous to those studied in other fields of research such as victimization (33,34)) in addition to a survivor bias: since respondents with higher exposure may have died sooner than those without it, they would be underrepresented among respondents older than 65 in this study. As for the memory biases, we may hypothesize that once a person has no longer a professional activity, it is more difficult for her/him to remind specific memories about occupational exposures.

To validate the relevance of DELCQ and its content validity, we conducted a case-control study comparing patients with known systemic autoimmune disorders from expert centers with controls matched by age range, sex and tobacco consumption (number of pack-years) from the ELIPSSilice2 survey. Our two sampling *scenarii* aimed to limit controls' selection bias. In both *scenarii*, the GES and OES from cases (both SSc and RA) were higher than those from controls. This result confirms findings from previous studies in the literature, supporting the relevance of the questionnaire and its ability to discriminate patients from controls.

Our results suggest that the difference between patients with autoimmune diseases and controls is substantially due to occupational exposure, as NOES did not differ between controls and patients (except for women and their matched controls in RA), in the two *scenarii*. The NOES were generally numerically higher than OES in both controls and patients. This suggests that score calculation methods identically applied to OES and NOES may not be completely relevant to quantifying non-occupational cumulative exposure. More specifically, since non-occupational exposures often occur without protection (e.g. mud bathing, clay eating, etc.), the points added to the NOES (considering this lack of protection) may create an excessive rise in the NOES vis-à-vis the OES. Moreover, considering a cumulative exposure of more than 5 years as a single category might also overestimate the NOES. A continuous quantification of the cumulative duration of exposure is theoretically preferable. But how could respondents actually answer? Using our calculation methods, we can trust the comparability of levels of (respectively) GES, OES and NOES between the various people (patients and respondents in the general population) in our samples, as in all cases inter-individual comparisons were made by adding up the same components of the exposure scores.

With regard to gender, significant lifetime overexposure to SiO_2 in the workplace appears for both women and men suffering from RA and SSc in comparison with their matched controls. Interestingly, NOES in women with RA were higher than in controls, unlike SSc patients. This unprecedented result might suggest that non-occupational silica exposure for women with RA could contribute to the pathogenesis and onset of their disease. We therefore subsequently explored which particular non-occupational situations are responsible for silica exposure in female RA patients in another study (Sigaux *et al.*, to be published).

Our inquiry method consisted of a retrospective reconstitution of exposure. This assessment is not equivalent to an empirical "live" measure of exposure (e.g. dust level measurements in the workplace). However, the latter measurements also have limitations, since they do not account for the presence/absence/effectiveness of potential respiratory protection equipment (35).

The questionnaire's methodological assets enable it to thoroughly screen sources of extra-occupational exposure. However, the cumulative dose of non-occupational exposure can be even more difficult to unearth for respondents than their cumulative occupational exposure. Considerable memory effort is required to estimate the time spent on hobbies likely linked to the exposures of interest and involving activities performed in short or discontinuous periods over a lifetime. The case-control approach is also limited insofar as cases (SSc or RA) were included from a single center for each disease, whereas controls were selected from the general French population

(national rolling census). Regional discrepancies may exist in the prevalence of silica exposure, and the design of the case-control study did not take these into account.

Moreover, data collection methods varied between RA and SSc patients (phone calls or face-to-face interviews by 4 trained evaluators) and control respondents (ELIPSSilice2 survey, self-administered questionnaires on tablets). We verified that this potential evaluation bias was limited, and particularly that a self-completion of the questionnaire offered sufficient guarantees in terms of specificity and sensibility. These results have been published elsewhere (36) showing that: a) The differences between the exposure scores of people reporting themselves as having a disease (ELIPSSilice1 & 2) and patients with a disease diagnosed by a physician (SSc, RA) suggested a lower sensitivity of self-questioning of exposures but without compromising the relevance of the self-collected data on exposure. b) Panelists interrogated twice (ELIPSSilice1 & 2) tended to have growing GES (above all because of an increase in OES), suggesting that, as time goes by between two waves of the survey, respondents manage to report new exposure that occurred in the meantime. c) In ELIPSSilice 1 & 2, respondents who self-declared having a disease had higher exposure scores as compared to those who did not declare any disease, confirming the results based on questionnaires with RA and SSc patients. d) To minimize false positive cases from too loose self-questioning on RA, we added the question: "Did a physician diagnose you with this disease using the term 'rheumatoid arthritis'?". All these data suggest that the self-completion of the questionnaire was not a major bias in this study.

One of DELCQ's major strengths is its methodological approach to questioning respondents. We sought to overcome several challenges in order to get sufficiently sensitive and specific responses, even when the questionnaire was self-administered. Questions were purposely numerous, and their wording was carefully chosen. The first challenge is that these relationships are part of a much broader landscape of knowledge uncertainty: science may be powerless when confronted with the production of ignorance more or less directly led by firms with huge economic interests in blurring and underestimating hazards (37–39). Second, at the individual level of knowledge, actual health hazards may be underestimated even in a well-known work environment. As observed with subcontracted workers (40), "virility as a defensive strategy to deny occupational risk", family arrangements, gambles on the future, and obviously the obligation to earn one's living may lead workers to "ignore" health hazards and corresponding preventive measures. Our questionnaire therefore includes some analogous questions multiple times to bring back factual memories, whether it is conducted by an external evaluator or self-administered.

CONCLUSION

Our results confirm that SiO_2 hazards *specifically* involve exposure *in occupational activities*. This makes a compelling case for medical training programs. Physicians should not overlook such occupational risks when recording their patients' medical histories, even for rare disorders such as SSc. Lifetime occupational exposure to SiO_2 is higher in RA and SSc patients *versus* the general population, suggesting it may be either an environmental cause of the diseases or a factor in the severity of the disease phenotypes, often observed in male patients, or even both (8, 39). Further research is needed on sex/gender-specific disease severity and SiO_2 overexposure in both RA and SSc. Moreover, some pieces of evidence keep accumulating about the deleterious role played by SiO_2 exposure in SSc male patients (42,43). Our results suggest for the first time that extra-occupational exposure to SiO_2 may contribute to the onset of RA in women.

Such results suggest that the sex variable should not be considered a final result, but rather that the differences between men and women should be probed. Differences between men and women in connective tissue diseases in terms of aetiology and severity should be considered as a "black box" (44) while deconstructing the gender gap. Uncovering different exposure levels and contexts between the sexes may participate in answering the question: *what* differentiates men and women with a systemic disease from both a biological and sociological perspective?

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Tables & Figures

Figure 1: Exposure scores from DELCQ, according to the age of ELIPSSilice1&2 panelists

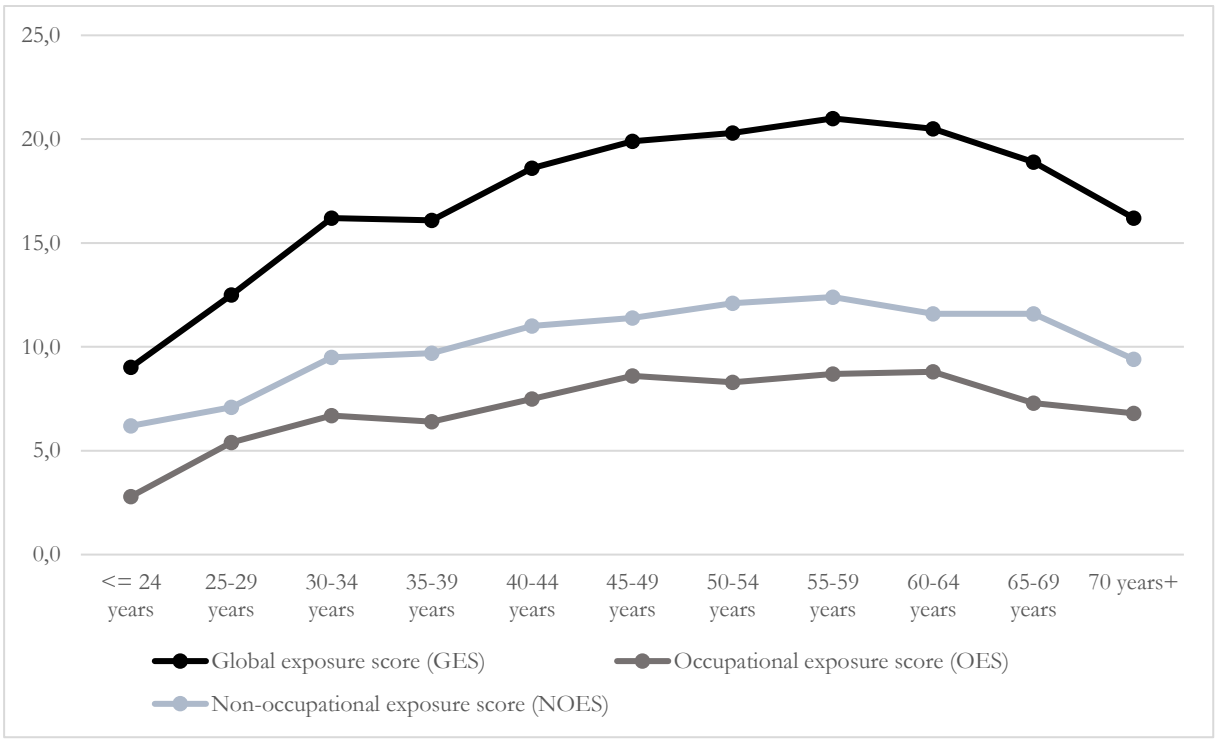

Table 1: Compared exposure scores from DELCQ between diagnosed (RA, SSc) patients and controls randomly sampled in ELIPSSilice2

Exposure scores		SSc Scenario #1[1]			SSc Scenario #2[2]			RA Scenario #1[1]			RA Scenario #2[2]		
		Patients (n=100)	**Controls£ (n=394)**	***p****	**Patients (n=100)**	**Controls £ (n=380)**	***p****	**Patients (n=97)**	**Controls £ (n=388)**	***p****	**Patients (n=97)**	**Controls £ (n=388)**	***p****
GES	Mean	27.4 (SD=19.5)	21.9 (SD= 21.0)	0.001	27.4 (SD=19.5)	21.9 (SD=21.2)	0.001	28.4 (SD= 17.3)	19.7 (SD=19.2)	$4.026*10^{-7}$	28.4 (SD=17.3)	19.9 (SD=17.5)	$4.626*10^{-7}$
	Median	23.0 (IQR=29. 0)	16.0 (20.0)		23.0 (IQR= 29.0)	17.0 (IQR=19. 0)		26.0 (IQR=25. 0)	15.0 (IQR=19. 0)		26.0 (IQR=25. 0)	15.5 (IQR=17. 5)	
OES	Mean	13.8 (SD= 15.2)	6.7 (SD= 13.4)	$2.068.10^{-10}$	13.8 (SD=15.2)	6.1 (SD= 13.2)	$1.186*10^{-11}$	13.1 (SD=12.8)	5.1 (SD= 11.1)	$<2.2*10^{-16}$	13.1 (SD=12.8)	5.1 (SD= 10.6)	$<2.2*10^{-16}$
	Median	9.5 (IQR=20. 0)	0.0 (IQR=8.0)		9.5 (20.0)	0.0 (IQR=6.0)		10.0 (15.0)	0.0 (IQR=5.0)		10.0 (IQR=15. 0)	0.0 (IQR=5.0)	
NOES	Mean	13.7 (SD= 9.7)	15.2 (SD=12.3)	0.60	13.7 (SD= 9.7)	15.8 (SD=1 2.3)	0.27	15.3 (SD=9.1)	14 .7 (SD=12.0)	0.17	15.3 (SD=9.1)	14.8 (SD=11.2)	0.23
	Median	12.0 (IQR=16. 5)	13.0 (IQR=17.0)		12.0 (IQR=16. 5)	13.0 (IQR=14. 0)		15.0 (IQR=13. 0)	12.0 (IQR=17. 0)		15.0 (IQR=13. 0)	13.0 (IQR= 14.0)	

£ELIPSSilice2 respondents are used as controls, matched to SSc and RA patients respectively on sex, age, and tobacco use (number of pack-years).

[1] Scenario #1 : controls were selected among people declaring "not having the disease the matched comparison is made with".

[2] Scenario #2 : controls were selected among people "declaring having (or having had) *none* of the chronic conditions (i.e. neither the disease the matched comparison is made with, *nor any other* chronic conditions evaluated in the questionnaire)".

* Wilcoxon test, level of significance $p<0.05$

GES: Global exposure score; OES: Occupational exposure score; NOES: Non-occupational exposure score; GES=OES+NOES

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Table 2: compared female and male patients' exposure scores from DELCQ in SSc and RA

Exposure scores		SSc (n=100)			RA (n=97)		
		Women (n=74)	**Men (n=26)**	***P****	**Women (n=77)**	**Men (n=20)**	***P****
GES	Mean	20.7 (SD=14.5)	46.5 (SD=19.7)	$1.27*10^{-7}$	25.3 (SD=15.0)	40.1(SD=20.7)	0.002
	Median	17.5 (IQR=20.0)	47.0 (IQR=23.0)		25.0 (IQR=21.0)	42.5 (IQR=28.0)	
OES	Mean	8.0 (SD=8.5)	30.0 (SD=18.3)	$3.37*10^{-9}$	9.6 (SD=9.0)	26.5 (SD=16.2)	$4.11*10^{-6}$
	Median	6.0 (IQR=13.0)	26.0 (IQR=22.0)		7.0 (IQR=11.0)	23.5 (IQR=16.5)	
NOES	Mean	12.7 (SD=9.7)	16.4 (SD=9.5)	0.08	15.7 (SD=8.9)	13.5 (SD=9.9)	0.31
	Median	11 (IQR=14.0)	15.5 (IQR=17.0)		15.0 (IQR=12.0)	12.0 (IQR=15.5)	

* Wilcoxon test, level of significance $p<0.05$

GES: Global exposure score; OES: Occupational exposure score; NOES: Non-occupational exposure ; GES=OES+NOES

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Table 3: Dust exposure scores from DELCQ in the general population (ELIPSSilice1 & 2, N= 2 911) according to the sex of the respondents

	Female respondents (N=1 519)	Male respondents (N= 1384)
GES		
Mean	13.2 (SD=14.0)	23.2 (SD=24.6)
Median	9.0 (IQR=15.0)	15.0 (IQR=27.0)
OES		
Mean	3.4 (SD=7.2)	11.7 (SD=18.0)
Median	0.0 (IQR=4.0)	4.0 (IQR=16.0)
NOES		
Mean	9.8 (SD=9.4)	11.5 (SD=10.6)
Median	7.0 (IQR=11.0)	9.0 (IQR=15.0)

We do not know the sex of 8 respondents: 1 519+1 384=2 903 among 2 911 ELIPSSilice1 & 1 respondents.

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Table 4: Compared dust exposure scores from DELCQ between diagnosed (RA, SSc) patients and controls randomly sampled in ELIPSSilice2 and stratified by sex

Exposure Scores		SSc Women (n=74)			SSc Men (n=26)			RA Women (n=77)			RA Men (n=20)		
		Patients (n=74)	Controls£ Scenario#1 (n=290)	*p**	Patients (n=26)	Controls£ Scenario#1 (n=104)	*p**	Patients (n=77)	Controls£ Scenario #1 (n=308)	*p**	Patients (n=20)	Controls£ Scenario #1 (n=80)	*p**
GES	Mean	20.7 (SD=14.5)	19.8 (SD= 17.7)	0.24	46.5 (SD=19.7)	27.6 (SD= 27.5)	$3.79*10^{-5}$	25.3 (SD=15. 0)	18.2 (SD=16.8)	$6.55*10^{-6}$	40.1(SD=20.7)	25.7 (SD=25.6)	0.00521
	Median	17.5 (IQR=20.0)	16.0 (IQR=17.0)		47.0 (IQR=23 .0)	19.5 (IQR=34.0)		25.0 (IQR=2 1.0)	14.0 (IQR=18.5)		42.5 (IQR=28.0)	17.5 (IQR=27.0)	
OES	Mean	8.0 (SD=8.5)	4.2 (SD=8.5)	$8.65*10^{-7}$	30.0 (SD=18. 3)	13.4 (SD=20.5)	$1.36*10^{-6}$	9.6 (SD=9.0)	3.7 (SD=7.5)	$8.28*10^{-14}$	26.5 (SD=16.2)	10.4 (SD=18.6)	$4.445*10^{-6}$
	Median	6.0 (IQR=13.0)	0.0 (IQR=5.0)		26.0 (IQR=22 .0)	4.5 (IQR=18.5)		7.0 (IQR=1 1.0)	0.0 (IQR=5.0)		23.5 (IQR=16.5)	2.5 (IQR=12.0)	
NOES	Mean	12.7 (SD=9.7)	15.6 (SD=11.9)	0.09	16.4 (SD=9.5)	14.2 (SD= 13.4)	0.1	15.7 (SD=8.9)	14.5 (SD=12.1)	0.045	13.5 (SD=9.9)	15.4 (SD=11.8)	0.66
	Median	11 (IQR=14.0)	13.0 (IQR=15.0)		15.5 (IQR=17 .0)	11.0 (IQR=19.5)		15.0 (IQR=1 2.0)	12.0 (IQR=16.0)		12.0 (IQR=15.5)	14.0 (IQR=20.5)	

£ELIPSSilice2 respondents are used as controls, matched to SS and RA patients respectively on sex, age, and tobacco use (number of pack-years).

[1] Scenario #1: controls were selected among people "declaring not having the disease the matched comparison is made with ».

[*] Wilcoxon test, level of significance $p<0.05$

GES: Global exposure score; OES: Occupational exposure score; NOES: Non-occupational exposure score; GES=OES+NOES

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