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1 **Title page**

2

3 ***TITLE of the article***

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

6

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39 All authors meet the following four ICMJE criteria:

- 40 - Substantial contributions to the conception or design of the work; or the acquisition,
41 analysis, or interpretation of data for the work; AND
- 42 - Drafting the work or revising it critically for important intellectual content; AND
- 43 - Final approval of the version to be published; AND
- 44 - Agreement to be accountable for all aspects of the work in ensuring that questions related
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52 **Data availability statement:** The data that support the findings of this study are available upon
53 reasonable request to the corresponding author.

54

55

56

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

58 ***Objectives***

59 Develop and validate a thorough exposure questionnaire to comprehensively explore crystalline
60 silica (SiO₂) exposure in the general population (gender-specific, occupational and non-
61 occupational) and in patients with autoimmune diseases (Rheumatoid arthritis (RA), Systemic
62 sclerosis (SSc)).

63 ***Methods***

64 Lifetime exposures to SiO₂ in occupational and non-occupational settings were assessed using a
65 thorough exposure questionnaire. The questionnaire was applied to a general population panel
66 (N=2,911) sampled from the French rolling census, and to unselected patients with SSc (N=100)
67 and RA (N=97). Global (GES), occupational (OES) and non-occupational (NOES) exposure
68 scores were assessed in SSc and RA patients, and compared to up to 4 controls from the general
69 population, matched by age group, sex and tobacco consumption.

70 ***Results***

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

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

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

80 ***Conclusion***

81 The lifetime SiO₂ exposure gap between RA and SSc patients and controls was substantially due to
82 occupational exposure. In both diseases, men had higher exposure scores than women.

83

84 **Clinical trial registration number (for all RCT's):** NA

85

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

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

89

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

91 1 – Patients with SSc and RA had significant lifetime occupational overexposure to SiO₂.

92 2 – Occupational exposure in men with SSc or RA was higher than in women.

93 3 – Physicians should carefully assess past silica exposure, which could unlock financial
94 compensation for patients.

95

96 **References** (up to 50): 44

97

98 **Tables/figures:** 5 included in the article

99 + 2 Texts, 1 Figure & 2 Tables in Supplementary Material

100

101 **Word count:** 3,885

102

103

104 **INTRODUCTION**

105 Crystalline silica (or silicon dioxide, SiO₂), mainly occurring as the polymorphs quartz (the
106 most common in nature and manufacturing processes), cristobalite and tridymite, is one of the
107 most ubiquitous environmental components.

108 Resulting from exposure to SiO₂, silicosis was initially defined in 1930 at a conference
109 jointly organized by the International Labour Organization and the Transvaal Chamber of Mines,
110 a South African mining-industry employer organization (1,2). Ensuing decades saw the
111 involvement of SiO₂ highlighted in pulmonary alveolar proteinosis and systemic autoimmune
112 diseases such as systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus (SLE), and
113 ANCA-associated vasculitis (AAV) (3–5). The link between RA and SiO₂ has been well
114 documented in large cohorts of construction workers (6). Exposure to SiO₂ may contribute to
115 “decreasing the threshold for the development of autoimmune disease in general”, but could also
116 trigger the onset of some clinical manifestations of these diseases (7). The association between SiO₂

117 and SSc, the rheumatic disease with the highest individual mortality rate, has been continuously
118 reported in several case-control and cohort studies (8,9). Studies conducted since 2000 have
119 strengthened the association of SiO₂ and systemic autoimmune diseases, especially for exposure
120 from cutting, polishing or bevelling new high-silica content materials (10,11), out of the mining
121 sector (12,13).

122 Large-scale case-control or cohort studies exploring the association between SiO₂ and
123 autoimmunity rarely (if ever) consider non-occupational exposures. The general difficulty of
124 producing a standard measure of “normal” exposure to crystalline silica (14) reflects the lack of
125 standardized questionnaires able to explore SiO₂ exposure as a whole, and to identify the sources
126 of exposure over a lifetime in the general population and in people with autoimmune diseases.

127 The objective of this study was to develop and validate a thorough exposure questionnaire
128 to comprehensively explore SiO₂ exposure in the general population (gender-specific, occupational
129 and non-occupational). First, we administered the questionnaire to a large representative sample of
130 the French general population (sampled from the general French rolling census). Next, we assessed
131 and compared silica exposure in patients diagnosed with SSc or RA versus the general population.

132

133 **MATERIAL AND METHODS**

134

135 **Assessment of exposure to mineral dusts**

136 *Designing the questionnaire*

137 The Dust Exposure Life-Course Questionnaire (DELCQ) mainly aimed to assess exposure
138 to SiO₂. To reach sufficient sensitivity, we prepared a list of questions based on the inventory of
139 exposure activities made by the Working Group on the Evaluation of Carcinogenic Risks to
140 Humans (15). To develop a thorough inquiry, we supplemented this large list of exposure activities
141 by broadening their spectrum with medical or statistical surveys of the general population (16–18).
142 We added in data from the literature on exposure to SiO₂ and inorganic particles in occupational
143 or environmental settings, including clinical case reports (on clay eating (19), exposure to cat litter
144 dust (20), talcum spreading on abraded skin (21), and air contamination by working clothes as in
145 the case of asbestos (22)), as well as metrological and epidemiological questions on the average
146 silica concentration in ambient air (14).

147 Drawing on lessons from the sociology of labor (23), we avoided asking people about pre-labelled
148 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 SiO₂, the

182 two modules also sought to quantify the exposure level according to the respondent's self-
183 assessment. For more than 95% of the questions, the respondent had to answer a first screening
184 question exploring an occupational or non-occupational setting *potentially* at risk of exposure to
185 SiO₂. If answered in the affirmative, one or more questions followed to assess whether the
186 respondent had been involved in specific exposure activities in this setting, and if so, the cumulative
187 duration of exposure in his/her life (<1 year; [1;5[years; >= 5 years) and the level of protection
188 (mainly respiratory but also cutaneous and ophtalmological) from dust he/she had used (from (i)
189 never protected or protection always ineffective; to iii) always effectively protected)
190 (**Supplementary Text 1**). A dust exposure score was then calculated based on the duration and
191 the effectiveness of protections against dust (see Suppl. Fig. S2 in (26)). We applied this inquiry
192 approach to most of the situations reviewed, predominantly occupational exposure (48 different
193 occupational scenarios and 18 non-occupational scenarios). Alternatively, the first relevant
194 question could directly focus on a specific exposure activity, without the first filter question about
195 the at-risk setting (**Supplementary Text 2**). Assessing the level of protection was not always
196 relevant, notably in non-occupational contexts. For instance, the use of talcum powder on abraded
197 skin was by definition not associated with cutaneous protection. In such (exceptional) situations,
198 the number of points we added to the dust score was equivalent to that of an exposure without
199 protection.

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

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

209

210 **Fieldwork and questionnaire processing**

211 ***1 – French general population***

212 *Presentation and processing*

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

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

219 *Exploration of self-declared RA*

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

226

227 ***2 – Populations of patients from expert centers, diagnosed with systemic autoimmune*** 228 ***diseases***

229 *Patient populations*

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

239

240 **Ethics**

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

246

247 **Statistical methods**

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

258

259

260 **RESULTS**

261

262 **1 – Exposure scores in the general population**

263 Among the 2,911 panelists who responded to ELIPSSilice1 only, ELIPSSilice2 only, or
264 ELIPSSilice1 & 2, the lifetime prevalence of self-declared SiO₂ exposure (i.e. a strictly positive
265 GES) was 90.7%, with a mean exposure level of 17.97 (SD=20.4), and a median exposure level of
266 12.0 (IQR=20.0) (**Supplementary Table 2**). The prevalence of exposure in occupational settings
267 (OES>0) was 46.0%, and the prevalence of exposure in non-occupational settings (NOES>0) was
268 87.9%.

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

273

274 **2 – Case-control comparison of SiO₂ exposure: respondents in the general population 275 *versus* patients diagnosed with systemic diseases**

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

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

285

286

287 **3 – Relationships between sex and SiO₂ exposure in SSc and RA**

288 Among patients diagnosed with SSc and patients diagnosed with RA, male patients had
289 significantly higher GES than female patients (**Table 2**). This difference stemmed from a
290 significantly higher exposure for male patients in occupational settings. In non-occupational
291 settings, NOES in female and male patients did not differ. The comparison of exposure levels
292 between SSc and RA by sex showed that SSc male patients had higher GES than RA male patients
293 as a result of higher OES, whereas female RA patients had higher GES than SSc female patients
294 by virtue of a higher NOES (**Table 2**). In the general population (ELIPSSilice1 & 2), median GES
295 in women and men were 9.0 (IQR=15.0) and 15.0 (IQR=27.0), respectively (**Table 3**). Median
296 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
297 (IQR=15.0) in both sexes, respectively.

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

305

306

307 **DISCUSSION**

308 This study extensively explored SiO₂ exposure in the French general population and in
309 populations with two autoimmune diseases repeatedly associated with this exposure in the
310 literature. The use of a novel inquiry tool based on social science and statistical skills enabled a
311 thorough assessment of lifetime silica exposure. Importantly, the questionnaire focused on the

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

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

316 The high prevalence of a history of exposure to silica found in this survey (90.7%) underscores
317 the ubiquity of occupational and non-occupational exposure to one of the most common mineral
318 components of the earth crust, when a sensitive questionnaire is used. The only French statistical
319 survey (SUMER, Medical Follow-Up of Exposure to Occupational Hazards) that has measured it
320 (in 1994, 2003, 2010, 2016-2017) considers only occupational exposure to SiO₂ in the general
321 population, and allows occupational physicians to select “yes” only for workers exposed during the
322 latest working week (29). This lack of systematicity (30) has yielded the excessively low finding that
323 a paltry 1.4% of salaried workers are exposed to silica (16).

324 Other nationwide studies on SiO₂ exposure (28,31,32) have also solely focused on occupational
325 exposure. The prevalence of SiO₂ exposure in those studies ranged from 17% (in men) (31) to
326 1.0% (in women) (28), depending on several parameters (e.g. cross-sectional survey *versus* cohort,
327 exposure assessed in current job *versus* all *cursus laboris*, assessment via exposure-job matrices). In
328 the Danish nationwide survey (31), higher exposure levels were associated with older age. The same
329 trend appeared in our work, although respondents over 64 years old reported lower OES than
330 patients aged 45-64. This could be attributable to the retrospective nature of the evaluation,
331 introducing memory biases (analogous to those studied in other fields of research such as
332 victimization (33,34)) in addition to a survivor bias: since respondents with higher exposure may
333 have died sooner than those without it, they would be underrepresented among respondents older
334 than 65 in this study. As for the memory biases, we may hypothesize that once a person has no
335 longer a professional activity, it is more difficult for her/him to remind specific memories about
336 occupational exposures.

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

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

359 With regard to gender, significant lifetime overexposure to SiO₂ in the workplace appears for
360 both women and men suffering from RA and SSc in comparison with their matched controls.
361 Interestingly, NOES in women with RA were higher than in controls, unlike SSc patients. This
362 unprecedented result might suggest that non-occupational silica exposure for women with RA
363 could contribute to the pathogenesis and onset of their disease. We therefore subsequently
364 explored which particular non-occupational situations are responsible for silica exposure in female
365 RA patients in another study (Sigaux *et al.*, to be published).

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

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

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

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

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

409

410 **CONCLUSION**

411 Our results confirm that SiO₂ hazards *specifically* involve exposure *in occupational activities*.
412 This makes a compelling case for medical training programs. Physicians should not overlook such
413 occupational risks when recording their patients' medical histories, even for rare disorders such as
414 SSc. Lifetime occupational exposure to SiO₂ is higher in RA and SSc patients *versus* the general
415 population, suggesting it may be either an environmental cause of the diseases or a factor in the
416 severity of the disease phenotypes, often observed in male patients, or even both (8, 39). Further
417 research is needed on sex/gender-specific disease severity and SiO₂ overexposure in both RA and
418 SSc. Moreover, some pieces of evidence keep accumulating about the deleterious role played by
419 SiO₂ exposure in SSc male patients (42,43). Our results suggest for the first time that extra-
420 occupational exposure to SiO₂ may contribute to the onset of RA in women.

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

427

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Tables & Figures

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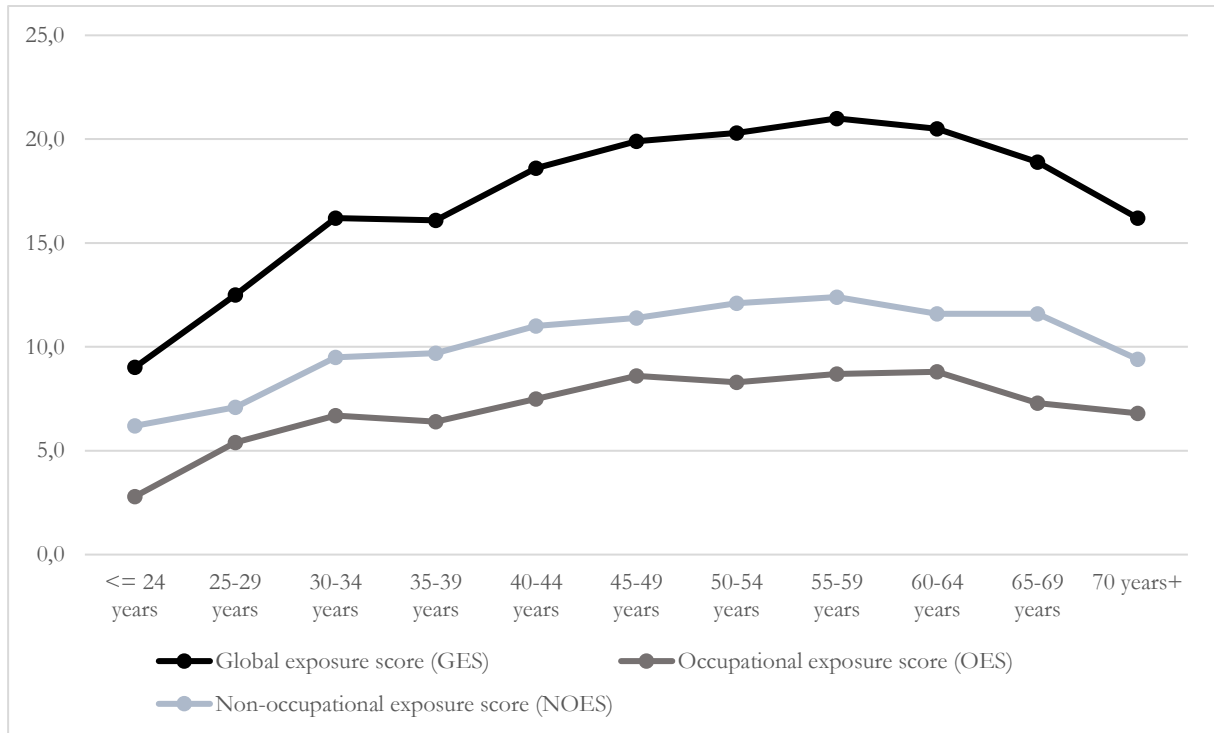
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Figure 1: Exposure scores from DELCQ, according to the age of ELIPSSilice1&2 panelists

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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)	<i>p</i> *	Patients (n=100)	Controls [£] (n=380)	<i>p</i> *	Patients (n=97)	Controls [£] (n=388)	<i>p</i> *	Patients (n=97)	Controls [£] (n=388)	<i>p</i> *
GES	Mean	27.4 (SD=19.5)	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)	
OES	Mean	13.8 (SD=15.2)	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 (IQR=15.0)		0.0 (IQR=5.0)	10.0 (IQR=15.0)	
NOES	Mean	13.7 (SD=9.7)	0.60	13.7 (SD=9.7)	15.8 (SD=12.3)	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)	

[£]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)	<i>p</i> *	Women (n=77)	Men (n=20)	<i>p</i> *
GES	Mean	20.7 (SD=14.5)	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)	
OES	Mean	8.0 (SD=8.5)	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)	
NOES	Mean	12.7 (SD=9.7)	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)	

* 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)

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

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)	<i>p</i> *	Patients (n=26)	Controls [‡] Scenario ^{#1} (n=104)	<i>p</i> *	Patients (n=77)	Controls [‡] Scenario ^{#1} (n=308)	<i>p</i> *	Patients (n=20)	Controls [‡] Scenario ^{#1} (n=80)	<i>p</i> *
GES	Mean	20.7 (SD=14.5)	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=21.0)		14.0 (IQR=18.5)	42.5 (IQR=28.0)	
OES	Mean	8.0 (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=1.0)		0.0 (IQR=5.0)	23.5 (IQR=16.5)	
NOES	Mean	12.7 (SD=9.7)	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=12.0)		12.0 (IQR=16.0)	12.0 (IQR=15.5)	

[‡]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