recognized by antinuclear antibodies, participating in the immune complex formation and the perpetuation of inflammation and autoimmunity. Interestingly, crystalline silica also specifically impairs efferocytosis in a dose-dependent manner,[9] and dietary omega-3 fatty acid restoring efferocytosis can limit silica-associated autoimmunity in mice.[10] These specific dose-dependent immune effects of crystalline silica are also in line with the epidemiological data from Boudigaard and colleagues.

Systemic diseases are still largely considered as diseases of unknown aetiology, whereas epidemiological data linking SSc or rheumatoid arthritis with silica exposure were published almost one century ago. The concordant results from nationwide epidemiological studies with *in vitro* and *in vivo* experiments may help in recognizing and endorsing this neglected pathogenic association. This is all the more important as new materials with high silica content, such as artificial stones used for example in the production of kitchen countertops, are associated with a recent unprecedented outbreak of autoimmune diseases, and more particularly of SSc in men. SSc is the rheumatic disease with the highest case-specific mortality. As there is still no disease-modifying drug for SSc, the recognition of a pathogenic link between SSc and silica in association with the prevention of such occupational exposure is mandatory. The better understanding of the pathogenic mechanisms linking SSc and silica, and the underlying causes of these gender/sex-related differences, may also help to identify new therapeutic targets in the future.

## Conflict of interest

None declared.

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# Authors' response to: Occupational exposure to respirable crystalline silica and autoimmunity: sex-differences in mouse models

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We thank Lescoat *et al.*[1] for their interest in our recent article reporting positive exposure response relations between quantitative measures of occupational exposure to respirable crystalline silica and incidence of autoimmune rheumatic diseases in men and in women.[2] We are grateful

**Table 1** Summary of eight studies providing sex-specific association between exposure to crystalline silica and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis

| Study, country | Study population (cases/controls by sex) | Exposure assessment | Outcome | Confounders accounted for | Odds ratios (95% CI)[a] | | Relative odds or rate ratios (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | | | Women | Men | |
| **Systemic sclerosis** | | | | | | | |
| Diot *et al.*, 2002 France[3] | General population, F: 69/138 M: 11/22 | Occupational history combined with blinded expert assessment and self-reported silica exposures | Medical records, ACR criteria | Age, smoking | 13.04 (1.54-110.66) | 3.62 (0.64-20.40) | 3.60 (0.23-56.36) |
| Bovenzi *et al.*, 2003 Italy[4] | General population, F: 46/153 M: 9/18 | Occupational history combined with blinded expert assessment and self-reported silica exposures | Medical records, ACR criteria | Age | 2.4 (0.4-15.5) | 1.2 (0.1-15.8) | 2.00 (0.08-45.41) |
| Maître *et al.*, 2004 France[5] | General population, F: 83/166 M: 10/40 | Occupational history combined with blinded expert assessment and self-reported silica exposures | Disease register ACR criteria | Age, education | No exposed cases | 0.9 (0.2-4.4) | – |
| Marie *et al.*, 2014 France[6] | General population, F: 22/66 M: 78/234 | Occupational history combined with blinded expert assessment and self-reported silica exposures | Medical records, ACR criteria | Smoking | 3.08 (0.40-23.49) | 8.30 (2.58-29.60) | 0.37 (0.03-3.99) |
| Boudigaard *et al.*, 2021[2] | General working population, F: 746/1 470 618[b] M: 252/1 541 416[b] | Lifelong occupational history combined with quantitative JEM | National health registries, ICD-8 and ICD-10 | Age, calendar year | 1.14 (0.95–1.36)[c] | 1.10 (1.03–1.18[c] | 1.04 (0.86-1.26) |
| **Rheumatoid arthritis** | | | | | | | |
| Turner *et al.*, 2000 UK[7] | Pottery and sandstone workers, F: 15/60 M: 43/172 | Occupational history within potteries combined with industry-specific JEM | Diagnoses from medical surveillance scheme | Smoking, parity (women), coal mining employment (men) | 1.13 (0.73-1.73) [d] | 0.71 (0.52-0.97) [d] | 1.59 (0.93-2.71) |

**Table .** (continued)

| Study, country | Study population (cases/controls by sex) | Exposure assessment | Outcome | Confounders accounted for | Odds ratios (95% CI)[a] | | Relative odds or rate ratios (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | | | Women | Men | |
| Ilar *et al.*, 2019 Sweden[8] | General population, F: 7622/77 902 M: 3634/37 064 | Occupational titles from national census combined with JEM | National health registries, ICD-10 | Age, county, calendar year | 1.2 (0.9-1.6) | 1.6 (1.4-1.7) | 0.75 (0.55-1.03) |
| Boudigaard *et al.*, 2021 Denmark[2] | General working population, F: 9190/1 470 129[b] M: 3490/1 541 217[b] | Lifelong occupational history combined with quantitative JEM | National health registries, ICD-8 and ICD-10 | Age, calendar year | 1.05 (0.98–1.11)[c] | 1.07 (1.05–1.10)[c] | 0.98 (0.92- 1.05) |
| **Systemic lupus erythematosus** | | | | | | | |
| Parks *et al.*, 2002 USA[9] | General population, F: 240/321 M: 25/34 | Occupational history combined with blinded expert assessment and self-reported specific exposures | Medical records, ACR criteria | Age, state, race, education | 3.3 (0.6-17.8)[e] | 6.0 (0.7-48.0)[e] | 0.55 (0.04-8.26) |
| Boudigaard *et al.*, 2021 Denmark[2] | General working population F: 1821/1 470 559[b] M: 255/1 541 465[b] | Lifelong occupational history combined with quantitative JEM | National health registries, ICD-8 and ICD-10 | Age, calendar year | 1.04 (0.89–1.22)[c] | 1.09 (1.01–1.17)[c] | 0.95 (0.80-1.14) |
| **Small vessel vasculitis** | | | | | | | |
| Boudigaard *et al.*, 2021 Denmark[2] | General working population F: 869/1 469 392[b] M: 749/1 539 809[b] | Lifelong occupational history combined with quantitative JEM | National health registries, ICD-8 and ICD-10 | Age, calendar year | 1.03 (0.82–1.29)[c] | 1.06 (1.01–1.11)[c] | 0.97 (0.77-1.23) |

JEM, job exposure matrix; F, female; M, male; ICD-8, 8th version of the International Classification of Diseases; ICD-10, 10th version of the International Classification of Diseases; ACR criteria, American College of Rheumatology classification criteria; CI, confidence interval.

[a]Odds ratio for ever vs never silica exposure unless else stated.

[b]Persons at risk.

[c]Rate ratio per 50 $\mu g/m^3$-years.

[d]Odds ratio per 1000 $\mu g/m^3$-years.

[e]Odds ratio for high vs no silica exposure.

for the new experimental and mechanistic evidence they present which shed important light on the possible mechanisms behind our epidemiological findings.

Our results suggest a less evident exposure response relation for women than for men. Lescoat *et al*. propose that this reflects a sex-dependent effect. They refer to experimental data supporting this interpretation.

In response to Lescoat *et al*., we searched the literature for articles presenting separate estimates for men and for women of the association between silica exposure and autoimmune rheumatic diseases. We identified seven additional studies, which assessed exposure differently from our study, i.e. largely based on occupational history combined with expert assessment and self-reports and not based on quantitative model estimates as was ours. Furthermore, all but one included few participants. We computed relative odds ratios for women versus men for each study and corresponding relative incidence rate ratios for our own published results. As can be seen from Table 1, the relative ratio estimates indicated no disease-specific pattern by sex.

We also analysed our combined dataset of men and women and included sex as an interaction term in the adjusted models of cumulative exposure (the principal exposure metric). The interaction term represents the log of the relative incidence rate ratio for women compared with men. After exponentiation, we found relative incidence rate ratio estimates very close to those computed from the published sex-specific estimates: 1.03 [95% confidence interval (CI) 0.85-1.25), 0.98 (95% CI 0.91-1.04), 0.98 (95% CI 0.82-1.16) and 0.97 (95% CI 0.77-1.23) for systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis, respectively.

In conclusion, these additional analyses indicate a less evident association between silica exposure and rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis for women than for men, whereas the opposite was suggested for systemic sclerosis. However, estimates were given with considerable uncertainty and earlier studies provided no support for sex-specific effects. Thus, there is still much to learn about possible sex-dependent effects of these diseases that dominate among women.

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## Conflict of interest

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