Exposure to air pollution as an environmental determinant of how Sjögren's disease is expressed at diagnosis

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Abstract

Objective

To analyse how the potential exposure to air pollutants can influence the key components at the time of diagnosis of Sjögren's phenotype (epidemiological profile, sicca symptoms, and systemic disease).

Methods

For the present study, the following variables were selected for harmonisation and refinement: age, sex, country, fulfilment of 2002/2016 criteria items, dry eyes, dry mouth, and overall ESSDAI score. Air pollution indexes per country were defined according to the OECD (1990-2021), including emission data of nitrogen and sulphur oxides (NO/SO), particulate matter (PM2.5 and 1.0), carbon monoxide (CO) and volatile organic compounds (VOC) calculated per unit of GDP, kg per 1000 USD.

Results

The results of the chi-square tests of independence for each air pollutant with the frequency of dry eyes at diagnosis showed that, except for one, all variables exhibited p-values <0.0001. The most pronounced disparities emerged in the dry eye prevalence among individuals inhabiting countries with the highest NO/SO exposure, a surge of 4.61 percentage points compared to other countries, followed by CO (3.59 points), non-methane (3.32 points), PM2.5 (3.30 points), and PM1.0 (1.60 points) exposures. Concerning dry mouth, individuals residing in countries with worse NO/SO exposures exhibited a heightened frequency of dry mouth by 2.05 percentage points (p<0.0001), followed by non-methane exposure (1.21 percentage points increase, p=0.007). Individuals inhabiting countries with the worst NO/SO, CO, and PM2.5 pollution levels had a higher mean global ESSDAI score than those in lower-risk nations (all p-values <0.0001). When systemic disease was stratified according to DAS into low, moderate, and high systemic activity levels, a heightened proportion of individuals manifesting moderate/severe systemic activity was observed in countries with worse exposures to NO/SO, CO, and PM2.5 pollutant levels.

Conclusion

For the first time, we suggest that pollution levels could influence how SjD appears at diagnosis in a large international cohort of patients. The most notable relationships were found between symptoms (dryness and general body symptoms) and NO/SO, CO, and PM2.5 levels.

Key words

Sjögren's syndrome, dryness, systemic, ESSDAI, air pollution, environment

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Competing interests: see page 2456.

Introduction

Ambient air pollution is a pressing public health challenge with profound implications for successive generations (1). Air contamination, especially particulate air pollution, is a ubiquitous environmental quandary characterised by minute particulates suspended aerially. This pollution encompasses an intricate amalgam of solid, liquid, and gaseous elements, predominantly sulphur dioxide (SO2), carbon monoxide (CO), nitrogen dioxide (NO2), and particulate matter (PM) (2). These elements invoke concern due to their detrimental impacts on human health and the broader environment. Sulphur oxides (SO) play a role in acid deposition, adversely affecting aquatic biomes and architectural structures and further imparting deleterious effects on flora. Emissions of Nitrogen oxides (NO) primarily originate from the combustion of fossil fuels at elevated temperatures and are pivotal in generating photochemical oxidants and atmospheric smog. Carbon monoxide poses health risks because it inhibits erythrocytes' efficient oxygen uptake. In tandem with NO, volatile organic compounds (VOC) are perceived as principal antecedents of photochemical atmospheric contamination. Particulate matter notably influences visibility degradation and strains human health as a vector for toxic metallic elements and other harmful compounds. Further distinction of PM is based on granular dimensions, leading to classifications such as PM10, PM2.5, PM1.0, and the minuscule ultrafine particles (PM0.1 or UFPs) (3).

Sjögren's disease (SjD) manifests as a systemic autoimmune condition, covering a plethora of clinical presentations (4). While its precise etiopathogenetic background remains enigmatic, accumulating data suggest a multifactorial origin (5), underscored by a dual interplay between genetic and environmental determinants (6). Familial clustering and associations with distinct genetic variants denote an inherited susceptibility towards SjD (7), potentially turning individuals to suffer aberrant immunological responses (8). Conceptualising this synergy between genetic predisposition and environmental exposure, one can use a "two-hit" paradigm. In those genetically predisposed, environmental triggers might aberrantly incite the autoimmune response, enabling the infiltration of autoreactive T and B lymphocytes that compromise exocrine glandular integrity and perpetuate an inflammatory cascade, resulting in tissue damage. Environmentally, viral agents have been postulated as the most plausible triggers of the disease, whereas endocrine imbalances may weigh immune responsiveness, amplifying vulnerability.

Furthermore, the disease's aetiopathogenetic process might be moulded by various extrinsic variables encompassing stress, geographical and climatic conditions, pollutants, and lifestyle choices (9). In synergy with genetic predisposition, these elements might anticipate the SjD initiation or, worse, its subsequent evolution. Intervening upon these environmental dynamics offers a supplementary therapeutic tier, potentially attenuating the risk or reducing the disease's severity amongst predisposed individuals. Despite considerable advancements in discerning the environmental interplay on the disease's progression, focused investigations into environmental factors still need to be conducted. Two pioneering studies from China have recently investigated the potential contributory role of atmospheric contaminants in SjD (10-12).

In the absence of studies carried out in international cohorts, the primary objective of the study was to examine how the key components of the disease phenotype at the time of diagnosis (epidemiological profile, sicca symptoms, and systemic disease) can be influenced by the potential exposure to air pollution in a large worldwide, multi-ethnic cohort of patients with primary SjD.

Material and methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry created in 2014 to take a worldwide picture of the main features of primary SjD using a data-sharing cooperative merging of pre-existing clinical SjD databases from leading centres in clinical research in SjD from five con-

tinents (see reference 14 for additional methodological details). The canters share a harmonized data infrastructure and conduct cooperative online efforts to refine already collected data in each center. Databases from each centre are harmonised into a single database by applying data-cleaning pre-processing techniques. The inclusion criteria consisted of fulfilling the 2002/2016 classification criteria for SjD (13). Exclusion criteria for considering SjD as a primary disease consisted of the presence of other systemic autoimmune diseases. The project was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

By January 2023, the participant centres had included 16,679 patients from 27 countries. The main disease features at diagnosis were retrospectively collected and analysed. For the present study, the following clinical variables at diagnosis were selected for harmonization and refinement: age, sex, country, 2002/2016 criteria items, and overall ESSDAI score. The age at diagnosis was defined based on the moment the attending physician confirmed inclusion criteria. Systemic involvement at diagnosis was classified and scored using the ESSDAI classification (14).

Air pollution indexes per country were defined according to the OECD. Stat platform (3, 15). The OECD collects data from three sources: 1) *THE Convention on Long-Range Transboundary Air Pollution* (LRTAP Convention), UNECE-EMEP emissions Database, WebDab 2023, as of August 2023. 2) National Inventory Submissions 2023 as of August 2023) to the *United Nations Framework Convention on Climate Change* (UNFCCC, CRF tables); and 3) Replies to the OECD Questionnaire on the State of the Environment and comments from member countries received before September 2023. This dataset provides selected information on national emissions of traditional air pollutants: emission data are based upon the best available engineering estimates for a given period; they concern artificial emissions of sulphur/nitrogen oxides (SO/NO), particulate matter (PM), carbon monoxide (CO) and volatile organic compounds (VOC). Data exclude non-artificial emissions and international aviation and maritime transport emissions. All variables were an estimated mean per country of the annual emissions of these six air pollutants from 1990-2021 calculated per unit of GDP, kg per 1000 USD. The GDP used to calculate intensities is expressed in USD at 2015 prices and PPPs.

Statistical analysis

The statistical analysis was conducted to understand the relationship between air pollution measurements (independent variables) and characteristics of SjD at diagnosis (dependent variables) across 23 countries. The independent variables were average levels of air pollutants (Nitrogen/Sulphur oxides, Carbon monoxide, Non-methane Volatile Organic Compounds, PM1.0, and PM2.5). The dependent variables were the key determinants that defined the disease phenotype at diagnosis (mean age, frequency of women affected, frequency of dry eyes, frequency of dry mouth, and systemic disease measured according to the ESSDAI score) were classified as dependent variables.

Table I. Mean age at diagnosis and the standard deviation of the age according to the country-ranked exposure to air pollutants.

Air pollutants	Age at diagnosis in high-exposed countries (mean, SD) (years)	Age at diagnosis in other countries (mean, SD) (years)	t-statistic	*p*-value
Sulphur/nitrogen oxides	52.55 ± 14.38	52.25 ± 14.77	1.18	0.238
Carbon monoxide	52.26 ± 13.87	52.61 ± 15.26	-1.39	0.166
Non-methane VOC	52.21 ± 13.71	52.61 ± 15.24	-1.63	0.103
PM1.0	52.93 ± 14.54	51.26 ± 14.38	6.38	<0.001
PM2.5	52.83 ± 14.46	51.38 ± 14.52	5.57	<0.001

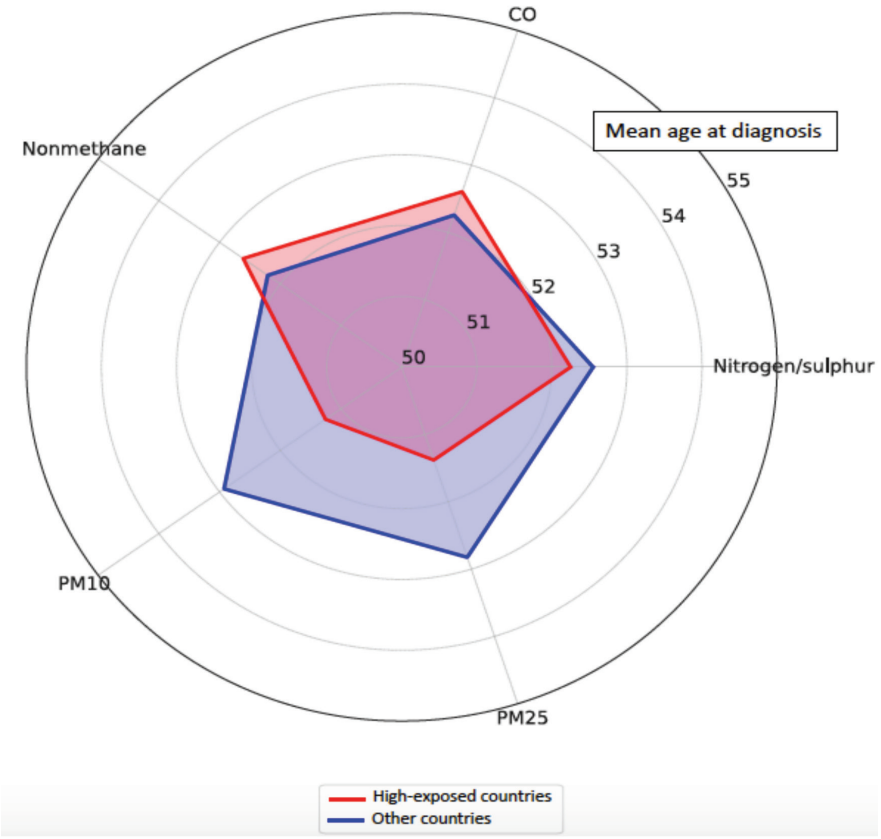

Fig. 1. Mean age at diagnosis according to the country-ranked exposure to severe air pollution (in red, mean age from people living in countries included among the top 10 worst exposed to air pollution; in blue, people living in other countries).

Table II. Results of the chi-square tests of independence for each air-pollutant-related variable with the frequency of dry eyes at diagnosis.

Air pollutants	Dry eyes in high-exposed countries (%)	Dry eyes in other countries (%)	Chi-square Statistic	*p*-value
Sulphur/nitrogen oxides	93.92%	89.31%	94.80	<0.001
Carbon monoxide	93.67%	90.08%	58.74	<0.001
Non-methane VOC	93.75%	90.43%	50.07	<0.001
PM1.0	93.30%	91.71%	11.22	0.001
PM2.5	94.02%	90.72%	49.46	<0.001

A dataset of pollution measurements was obtained from the OECD for 23 different countries. The air pollution variables were defined as dichotomous variables according to whether each country is ranked (yes or not) among the ten countries with the most significant pollution levels (estimated mean of the annual emissions of each pollutant during the period 1990-2021 in each country per unit of GDP, Kg per 1000 USD). Data cleaning was performed to ensure the accuracy and integrity of the dataset. The frequency of observations in each non-numeric category was analysed, and the characteristics of numeric variables were reviewed. This process helped identify and correct inconsistencies and mis-encoded values. The chi-square test of independence was used to analyse the association between categorical variables. The results were represented in tables with frequencies provided as the number of observations and the percentage of the total for each category. Independent two-sample t-tests were applied to compare categorical and continuous variables. All analyses were conducted by MRC using ChatGPT 4.0 Advanced Data Analysis as co-pilot, which used Python and the libraries *Pandas, Numpy, Scipy, Matplotlib, Seaborn,* and *Sklearn*. The code was written and executed in an environment with internet access turned off to ensure privacy and data security using a Jupyter Notebook, an open-source web application.

Results

Upon refining the dataset through data-cleaning techniques and excluding individuals from countries absent in the OECD database, our study database encompassed 16,042 patients spanning 23 countries. The patient cohort predominantly consisted of females (14,987 or 93.4%), with an average age at the time of primary SjD diagnosis being 51.74 (SD 14.47) years. About sicca symptoms, dry eye, and dry mouth frequencies were 90.9% and 92.1%, respectively, while the cohort's average ESSDAI score at diagnosis was 6.92 (SD 7.49).

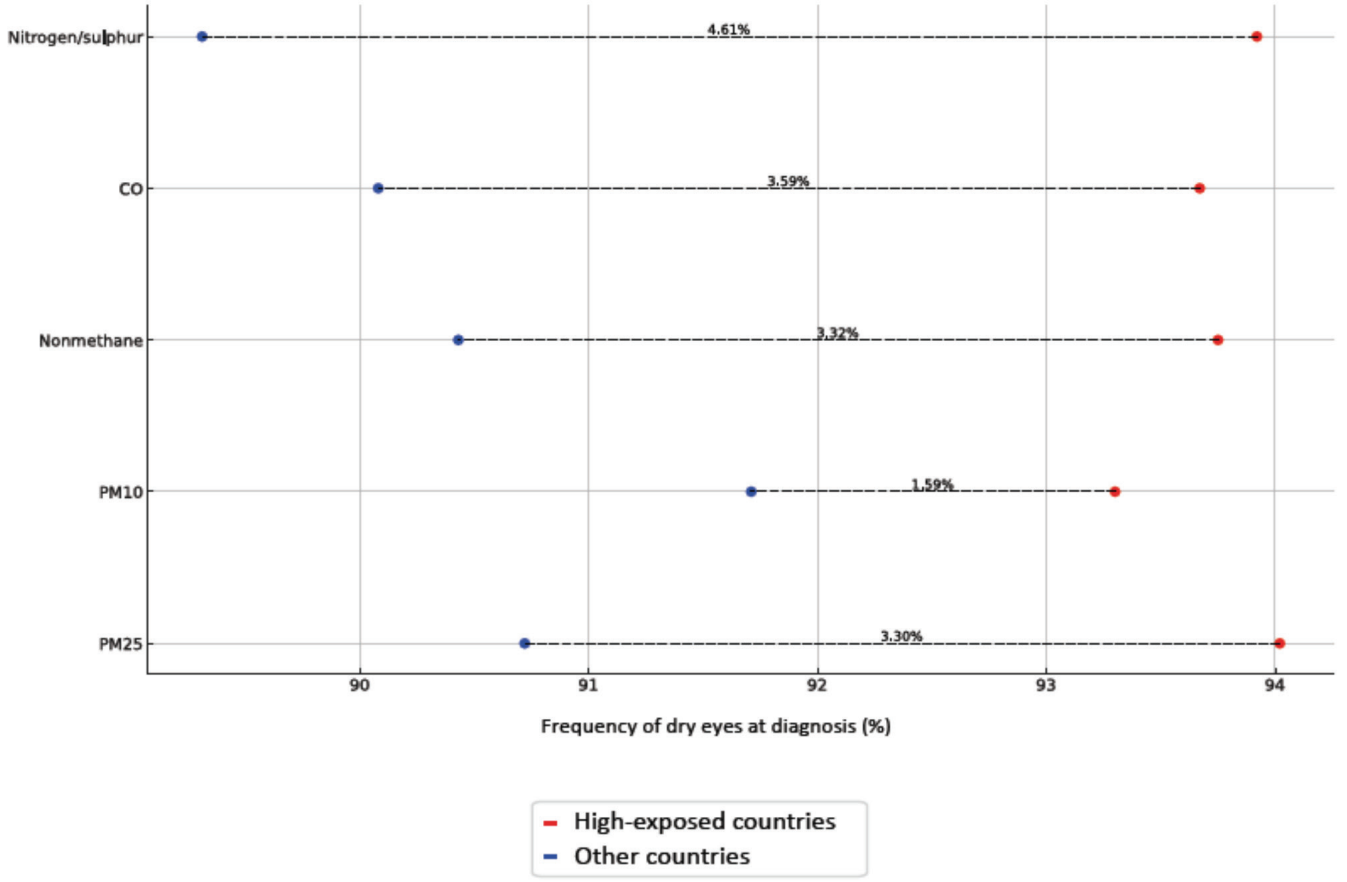

Fig. 2. Percentage difference in the frequency of xerophthalmia in people living in countries included among the top 10 worst exposed to air pollution (red bars) in comparison with people living in other countries (blue bars).

Table III. Results of the chi-square tests of independence for each air-pollutant-related variable with the frequency of dry mouth at diagnosis.

Air pollutants	Dry mouth in high-exposed countries (%)	Dry mouth in other countries (%)	Chi-square Statistic	*p*-value
Sulphur/nitrogen oxides	93.60%	91.55%	20.40	<0.001
Carbon monoxide	92.41%	93.09%	2.21	0.137
Non-methane VOC	93.38%	92.17%	7.23	0.007
PM1.0	93.17%	93.20%	0.00	0.984
PM2.5	93.34%	92.70%	1.89	0.169

a) Impact of air pollution on demographic characteristics

Supplementary Table S1 presents the results of the chi-square tests of independence for each air pollutant with the frequency of women affected by the disease living in countries included in the top 10 rank of worse pollution compared to people living in other countries. The results showed that all *p*-values were above 0.05, indicating that none of the correlations were statistically significant at the 5% level.

Table I shows the mean age at diagnosis relative to the country's exposure grading for each air pollutant. People from countries with elevated exposure to PM (occupying top positions in the OECD ranking) had an average age at diagnosis marginally more significant (approximately 1.5 years) than those in other countries. For the other air pollutants, *p*-values surpassed 0.05, signalling no significant correlations at the 5% threshold (Fig. 1).

b) Influence of air pollution on dryness manifestation

Table II presents the results of the chi-square tests of independence for each air pollutant with the frequency of dry eyes at diagnosis. Except for one, all variables exhibited *p*-values <0.0001. The most pronounced disparities emerged in the dry eye prevalence among individuals inhabiting countries with the worst NO/SO exposures – a surge of 4.61 percentage points compared to other countries. This was followed by CO (3.59 points), non-methane (3.32 points), PM2.5 (3.30 points), and PM1.0 (1.60 points) exposures (Fig. 2).

Table III displays the chi-square test results concerning each air pollutant and the frequency of dry mouth at diagnosis. Remarkably, individuals residing in countries with the worst NO/SO exposure exhibited a heightened frequency of dry mouth by 2.05 percentage points (p<0.001), followed by non-methane exposure (1.21 percentage points increase, p=0.007). Noteworthy, CO, PM2.5, and PM1.0 exposures did not evidence significant variances (Fig. 3).

c) The interplay between air pollution and systemic disease

Table IV presents the results of the

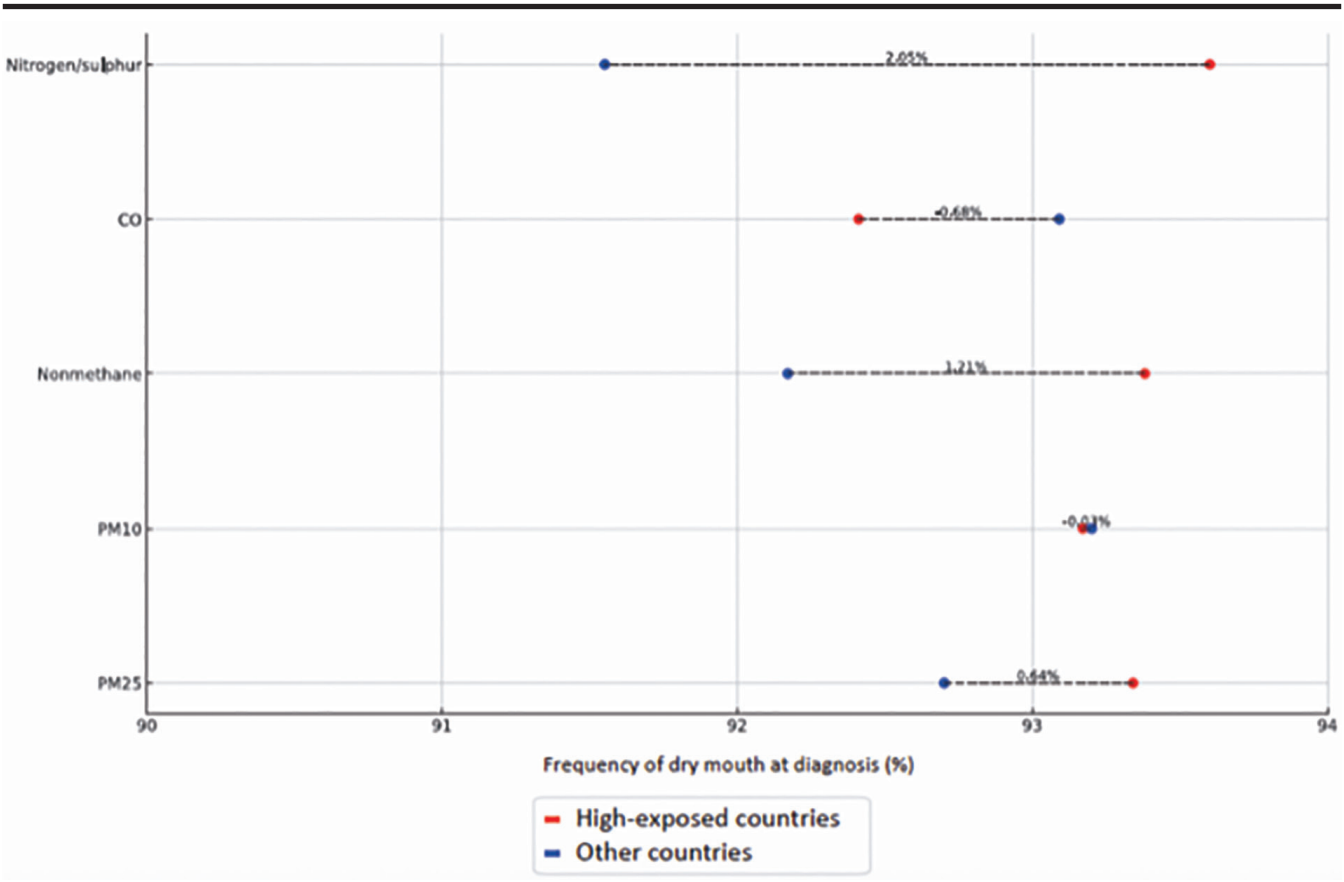

Fig. 3. Percentage difference in the frequency of xerostomia in people living in countries included among the top 10 worst exposed to air pollution (red bars) in comparison with people living in other countries (blue bars).

t-tests contrasting mean ESSDAI scores at diagnosis concerning exposure rankings of each air pollutant. Individuals inhabiting countries with high levels of exposure to NO/SO, CO, PM1.0, and PM2.5 pollutant levels documented a higher mean global ESSDAI score relative to those living in other countries (all *p*-values <0.001) (Fig. 4a-d). Conversely, people living in countries with elevated non-methane and PM 1.0 exposure revealed a weak association (*p*-values at 0.049 and 0.084, respectively). When systemic disease was stratified according to DAS into low, moderate, and high systemic activity tiers, a heightened proportion of individuals manifesting moderate to severe systemic activity was observed in countries with the worst exposure to NO/SO, CO, PM1.0, and PM2.5 pollutants (Table V) (Fig. 5).

Table IV. Results of the t-tests comparing the mean ESSDAI scores measured at the time of diagnosis according to the country-ranked exposure to each air pollutant.

Air pollutants	Mean ESSDAI score at diagnosis in high-exposed countries	Mean ESSDAI score at diagnosis in other countries	t-statistic	*p*-value
Nitrogen	7.2 ± 8.03	6.64 ± 6.92	4.7	<0.001
CO	7.55 ± 8.44	6.4 ± 6.56	9.55	<0.001
Non-methane	7.07 ± 8.19	6.82 ± 7	2.08	0.037
PM1.0	7.12 ± 8.05	6.71 ± 6.88	3.41	<0.001
PM2.5	7.36 ± 8.19	6.52 ± 6.8	6.97	<0.001

Discussion

We have reported that the average air pollution recorded in countries over the last 30 years might have a role in shaping the main characteristics of SjD at the time of their diagnosis. The most notable relationships were found between the frequency of symptoms (dryness and systemic features) and NO/SO, CO, and PM levels. There was also a weak association with non-methane levels. For the first time, we suggest pollution levels could influence how SjD appears at diagnosis in the largest reported cohort of people with SjD.

Air pollution's global effect is evident; it was responsible for about 7.6% of all deaths worldwide in 2015, making it a top-five risk factor (10). One primary health concern tied to outdoor air pollution is its harmful impact on our respiratory and cardiovascular systems, especially particles from burning fossil fuels, cars, and other human activities (16). Research also hints that exposure to PM2.5 can lead to several skin diseases, including eczema, acne, and psoriasis (12). The impact of polluted air might even go beyond this, with new evidence suggesting it plays a part in autoimmune diseases (2). Specific components, like silicon in the air, can lead to an imbalance in immune cells, which are vital in these diseases (2). While we see more evidence linking air pollution to these conditions, we still need to understand how it works fully (17).

Exposure to atmospheric pollutants has consistently been linked to an elevation in the incidence and severity of various autoimmune diseases, including both organ-specific and systemic conditions (18). Several studies have demonstrated a significant association between industrial emissions, including but not limited to PM2.5, NO2, and SO2, and the onset of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory myopathies, vasculitis, and undifferentiated connective tissue disease (1, 2, 19, 20). In the context of SLE, Rezayat *et al*. (21) published a comprehensive meta-analysis including six studies delineating a positive correlation between an incremental six-day exposure to PM2.5 and the systemic lupus erythematosus disease activity index (SLEDAI). However, no association was identified between the atmospheric presence of CO, NO_2, SO, PM2.5, and PM10 and the hospitalisation rates of SLE patients. About systemic sclerosis, Roeser *et al*. (22) found no correlation between exposure to particulate matter (PM10, PM2.5), NO_2, and diagnostic severity or disease progression. Conversely, Schioppo *et al*. (23) reported that PM10 and PM2.5 significantly exacerbated Raynaud's phenomenon severity during the initial four-day period before evaluation. Systemic vasculitis, especially antineutrophil cytoplasmic antibody (ANCA) vasculitis (20) and Kawasaki disease, have also been subjects of study. A recent population-based investigation in Korea analysing 51,486 paediatric cases reported a positive correlation between exposure to PM2.5 and SO_2 and the incidence of Kawasaki disease (24).

Several investigations have assessed the impact of air pollutants on dry eye disease (DED), one of the cardinal symptomatic components of SjD. Pollutants quantified by aerosol optical depth and atmospheric pressure have emerged as prominent risk factors for DES, particularly in metropolitan regions. Contrastingly, elevated humidity and wind speed displayed an inverse association with DES (25). Comprehensive reviews have suggested a probable link between pollutants, notably NO_2 and CO, and ocular discomfort and DES manifestations (26). At the same time, individuals with higher exposure to air pollution experience more pronounced ocular discomfort and greater tear film instability (27). Furthermore, research from Taiwan unveiled a substantial correlation between ambient NO_2 concentrations and DES (19). Severe air pollution has been proven to detrimentally impact the lipid layer thickness of the tear film in DED patients (28). Galperin *et al*. (29) reported ocular surface abnormalities and eye irritation related to air pollution using exposure to NO in the Metropolitan Area of Buenos Aires. These studies support the harmful effects of air pollution on ocular health, particularly in causing or exacerbating dry eye symptoms (10, 25, 26, 28, 30, 31). In stark contrast, no research has explored the potential effects of air pollution on oral dryness.

Our results suggest a potential link between exposure to worse air pollutants and a higher frequency of dry eye symptoms reported at the time of SjD diagnosis and, to a lesser extent, a higher frequency of dry mouth symptoms. A population-based cohort study in China reported that CO, NO, and CH4 exposure was associated with a

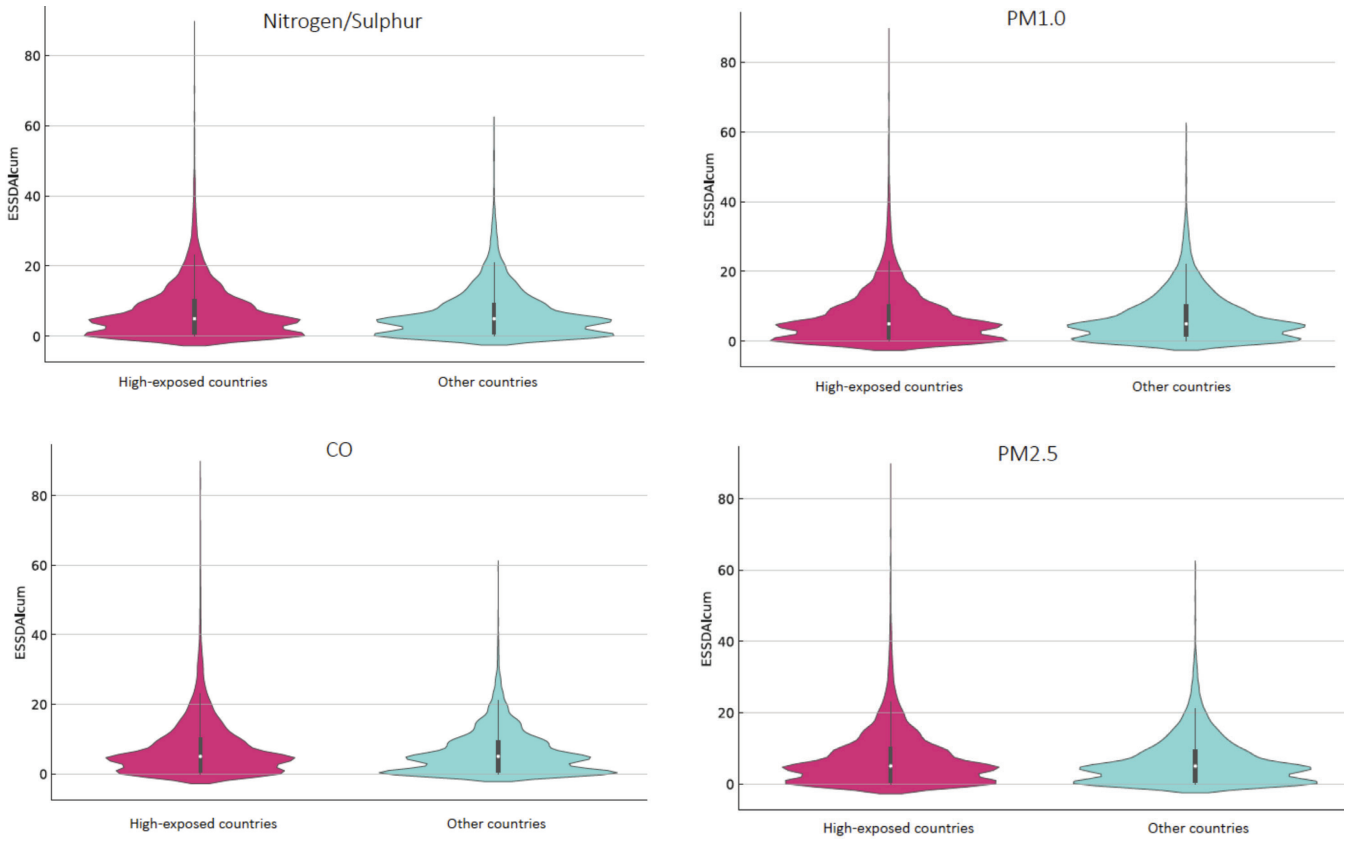

Fig. 4. Mean ESSDAI score at diagnosis in people living in countries included among the top 10 worst exposed to air pollution (red) in comparison with people living in no-risk countries (blue).

Table V. Systemic disease stratified according to DAS into low, moderate, and high systemic activity levels according to the country-ranked exposure to each air pollutant.

Air pollutants	High-exposed countries			Other countries				
	People with low DAS (%)	People with moderate DAS (%)	People with high DAS (%)	People with low DAS (%)	People with moderate DAS (%)	People with high DAS (%)	Chi-square Statistic	*p*-value
Nitrogen	46.40	37.47	16.13	49.01	37.18	13.81	15.81	<0.001
CO	46.29	36.55	17.16	48.86	38.28	12.86	46.72	<0.001
Nonmethane	48.17	36.27	15.56	46.87	38.31	14.82	5.93	0.0515
PM1.0	46.87	37.28	15.85	47.03	38.26	14.71	44.59	<0.001
PM2.5	45.39	38.00	16.61	49.58	36.77	13.65	43.78	<0.001

higher risk of SjD. Compared to those exposed to the lowest concentration levels, the HRs for SjD were 2.04, 1.86, and 2.21 for those exposed to high CO, NO, and CH4 levels, respectively. The cumulative effect of air pollution on SjD was time-dependent, and the correlation remained significant even after adjusting for variables such as age, sex, annual income, and urbanisation levels (11).

We also found a significant association between worse expositions to air pollutants and severe systemic disease, particularly in individuals residing in regions with elevated NO/SO, CO, and PM levels. No previous studies have analysed a potential association between air pollution and systemic SjD, which is related to an increased risk of morbidity and mortality (32, 33), especially in young-onset disease (34), and requiring intensive immunosuppressive therapies (35). However, a couple of recent studies carried out in China have linked air pollution with disease severity. The first study (10) reported a heightened risk of outpatient visits for SS following exposure to PM2.5 or NO, a risk more pronounced during the colder seasons, suggesting the influence of climate changes related to drier environmental conditions prevalent during colder months, which have been shown to exacerbate tear function issues in SS patients by augmenting inflammatory activity promptly (36). The second study consisted of a time-series study from the city of Hefei, which reported that exposure to PM2.5 and PM10 was significantly linked to an elevated risk of hospitalisations for SS and pointed out the vulnerability of female patients to PM2.5 and PM10 exposure, especially during the cold season possibly due to lower levels of humidity (12).

The statistical analyses conducted in this study serve as a preliminary investigation into the relationships between pollution levels and patient charac-

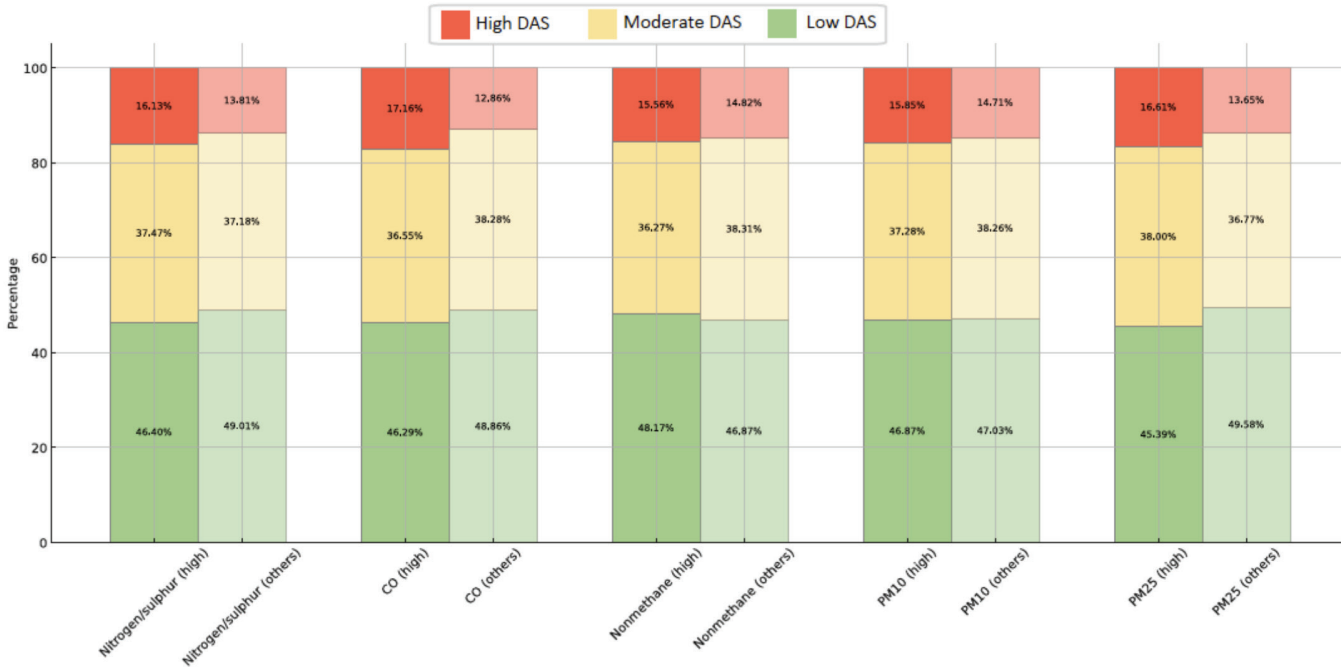

Fig. 5. Systemic disease stratified according to DAS into low, moderate, and high systemic activity tiers in people living in countries included among the top 10 worst exposed to air pollution *vs*. those living in no-risk countries.

teristics. Although the strength and direction of the correlations provided insights into potential associations between pollution levels and patient characteristics, no causal conclusions can be drawn from the results, and some limitations should be considered as this was an observational study. The analyses did not control for potential confounding variables, and other factors not included could also influence these variables. Air pollution is ubiquitous but varies across locations due to various elements, including climate change impacts, urbanicity levels, and proximity to significant roadways (37). Additionally, the data represents aggregated country-level statistics, which may not accurately reflect the experiences of individual patients. The emission estimation methods, such as emission factors and reliability, the extent of sources and pollutants included in estimations, etc., may differ from country to country. Another potential issue is temporality since the analyses assume that the geographic variation of air pollutants estimates was relatively constant for the 1990-2021 study period. Pollutant levels may have decreased or increased locally with the closure or opening of new industrial sources and other land-use changes, such as expanding road networks and residential populations, as Bernatsky *et al*. pointed out (38).

Our results suggest that people living in countries highly exposed to air pollutants more frequently manifest symptoms of dryness (especially at the ocular level) at the diagnosis of the disease, suggesting a possible cause-effect relationship between pollution and symptoms of discomfort suggestive of dryness. The same occurs with the systemic involvement of the disease at diagnosis, whose frequency is significantly higher in people who live in countries exposed to the worst levels of air pollution, concerning not only a higher average ESSDAI score, but also a higher frequency of moderate and severe systemic manifestations. This suggests a plausible relationship between environmental pollutants and the key symptoms of SjD, both glandular and systemic. A multidisciplinary strategy encompassing foundational science and public policy directives is imperative to effectively mitigate the health implications of air pollution. Integrating advanced analytical tools using big data and AI, coupled with extensive research, is paramount to comprehending the intricate mechanisms linking environmental factors and the phenotype of SjD.

Affilations

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Competing interests

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