Associarions Between Fine Particulate Matter (PM2.5) and Childhood-Onset Systemic Lupus Erythematosus

Chen-Hao Mai  
Children's hospital, china medical university hospital

Yen-Ju Shih  
Rheumatology and immunology center, department of internal medicine, china medical university hospital

Cheng-Li Lin  
management office for health data, china medical university

Lei Wan  
school of chinese medicine, China Medical University

Chang-Ching Wei  (weilonger@gmail.com)  
Children's Hospital, China Medical University Hospital; School of Medicine, China Medical University  
https://orcid.org/0000-0003-4835-3246

Research

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Abstract

Background:

Fine particulate matter (PM2.5) has been linked to induction of oxidative stress as well as pulmonary and systemic inflammation. We hypothesized that ambient PM\textsubscript{2.5} variation would be associated with the occurrence of childhood-onset systemic lupus erythematosus (cSLE).

Methods:

We collected data from the Taiwan National health insurance research database and linked these data to the Taiwan Air Quality-Monitoring Database. Children <18 years old, identified from January 1, 2000 were followed up until the first diagnosis of cSLE was made or until December 31, 2012. The daily average PM\textsubscript{2.5} was categorized into four quartile-based groups (Q1-Q4). We measured the incidence rate, hazard ratios (HRs), and 95% confidence intervals for cSLE stratified by the quartiles of PM2.5 concentration using Cox proportional hazards models adjusted for age, sex, monthly income, and urbanization.

Results:

A total of 394 children (0.16%) were newly diagnosed with cSLE during the observation period. The incidence rate for cSLE increased with PM2.5 levels, from 4.7 (Q1) to 21.9 (Q4) per 100,000 person-years. Compared with those exposed to the concentrations in the Q1 level, the adjusted HR from Q2 to Q4 for cSLE increased with PM\textsubscript{2.5} exposure concentrations from 2.74 to 4.23.

Conclusions:

The present study provides evidence that long-term variations in PM2.5 levels are risk factors for the development of cSLE.

Introduction

A diagnosis of childhood-onset systemic lupus erythematosus (cSLE) is made when individuals aged less than 18 years develop SLE. [1] cSLE accounts for 10%-20% of all SLE cases. Compared with adult-onset SLE, cSLE has a worse clinical course with significantly more lupus nephritis, hematological disorders, neurologic disorder, polyarthritis, mucocutaneous involvement, and photosensitivity. [2] Although the etiology of SLE remains unknown, it is multifactorial, including genetic, hormonal, immunologic, and environmental factors. Several environmental factors are reported to be associated with SLE, such as silica exposure, current cigarette smoking, exogenous estrogens, ultraviolet light, solvents, pesticides, heavy metals, and air pollution. [3]

There is a growing interest in the role of air pollution on inflammatory diseases, especially concerning particulate matters (PM). Sources of PM are mostly from human activities, including traffic and industrial emissions. [4] Fine PM (with a median diameter < 2.5 mm, PM2.5) are more toxic than other inhalable
particles because they can reach deeper areas of the respiratory tract and can be absorbed into the bloodstream through alveolar capillaries, resulting in a regional and even systemic, inflammatory process. [5, 6] Previous studies reveal that PM2.5 may be associated with acute and chronic lower respiratory diseases, cerebrovascular diseases, ischemic heart diseases, and lung cancer. [4]

Several studies have demonstrated that air pollution enhances the risk of autoimmune diseases in children. Although it is not clearly known what factors play a role in the pathogenesis of cSLE, it has been reported that exposure to SO\textsubscript{2} and O\textsubscript{3} lead to an increase in pediatric rheumatic diseases hospitalizations, and exposure to PM10, NO\textsubscript{2}, and CO may increase the risk of disease activity in cSLE. [6, 7] Moreover, maternal exposure to tobacco and air pollutants during pregnancy is associated with cSLE. [7] Recently, a study from Brazil demonstrated that short-term exposure to both indoor and outdoor PM2.5 was associated with increases in airway inflammation and systemic inflammation in cSLE patients. [8] However, these studies only assess the exposure to PM2.5 and the disease activity and hospitalization over a short period of time. There are limited studies examining the association between PM2.5 variation and the incidence of cSLE over a long period of time. Therefore, our objective was to evaluate the effects of air pollution on the risk of developing cSLE in Taiwan from 2000–2012.

Methods And Materials

Data Source

The data used in the current study were sourced from the Children file, a representative subset of data that includes data from half of all children randomly selected from the year 2000 registry of beneficiaries of the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD was established in March 1995 and includes detailed information, such as outpatient visits, hospital admissions, prescriptions, procedure, and diagnosis of disease, based on the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM), from 99% of the 23 million enrollees in Taiwan (http://www.nhi.gov.tw/english/index.aspx). The data were analyzed anonymously. This study has been approved by the Institute Review Board of China Medical University Hospital (CRREC-103-048) and complies with the principles outlined in the Helsinki Declaration.

Study population, outcome of interest, endpoints, and confounding factors

We identified children < 18 years old from January 1, 2000, to December 31, 2012. Children who had missing data and were diagnosed with SLE before the baseline were excluded. SLE was defined by at least 3 records of ICD-9-CM code 710.0 made in any diagnosis field during the inpatient or ambulatory claim process, as our outcome of interest. The Taiwan National Health Insurance (NHI) has classified SLE as a catastrophic illness, and the diagnosis of SLE must be confirmed by a board-certified specialist and be reviewed and approved by the Taiwan NHI. All participants were followed from baseline until the diagnosis of SLE was made, or patients withdrew from the NHI, or until December 31, 2012. In this study,
the mean standard deviation (SD) follow-up duration in SLE patients was 11.2 (2.32) years. The confounding factors were age, sex, urbanization level of residence, and monthly income. Urbanization level was defined based on population density and was stratified into four levels, from the highest density (Level 1) to the lowest density (Level 4). Monthly income was classified into 4 groups; < NT$14,400, NT$14,400–18,300, NT$18,301–21,000, and > NT$21,000.

**Exposure measurement**

The Taiwan Air Quality Monitoring Network (TAQMN) (http://taqm.epa.gov.tw/taqm/en/PsiMap.aspx) was established by the Taiwan Environmental Protection Administration (TEPA) in 1993 (http://www.epa.gov.tw/) and consists of 74 monitoring stations around the island. The monitoring stations were fully automated and provided daily readings of PM2.5. For each day, air pollution data were extracted from all monitoring stations and averaged. The databases of air pollutants were obtained from the Taiwan Air Quality-Monitoring Database (TAQMD), released by the TEPA. The NHIRD and the TAQMD were linked by the insurant living area and the air quality-monitoring stations’ location. The living area for each insured child was defined based on the sought treatment for the common cold (acute nasopharyngitis: ICD-9-CM code 460). A daily average air pollutant concentration was calculated by dividing the cumulative daily air pollutant concentration by the duration from 2000 to the endpoint for each study participant. The daily average air pollutant concentrations were categorized into 4 groups based on quartiles, namely Q1, Q2, Q3, and Q4. PM$_{2.5}$ was categorized as Q1 (< 29.5 µg/m$^3$), Q2 (29.5–33.3 µg/m$^3$), Q3 (33.3–41.1 µg/m$^3$), and Q4 (> 41.1 µg/m$^3$).

**Statistical analysis**

The demographic categories in the present study included age, sex, urbanization level of the residential area, and the daily average of exposure to air pollutants. To test the distributed difference among daily average concentrations of PM2.5 by quartile and urbanization, a $\chi^2$ test was used. The Kaplan–Meier method was used to estimate the proportion of study subjects who did not suffer from SLE during the follow-up period, among the different quartiles of PM2.5 level. The incidence density rate of cSLE (per 100,000 person-years) was counted by each quartile of daily average concentrations of PM2.5. A Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for SLE in the Q2–Q4 levels for air pollutant concentration, compared to the lowest one (Q1). A multivariable model was adjusted for age, sex, monthly income, and urbanization. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC) and the Statistical Package for the Social Science (Version 15.1; SPSS Inc, Chicago, IL). All statistical results were considered statistically significant when 2-tailed P values were < 0.05.

**Results**

A total of 394 children (0.16%) were newly diagnosed with SLE among a cohort of 244,607 children from January 1, 2001 to December 31, 2012. The demographic factors of the study subjects are shown in Table 1. The mean age of participants was 6.09 years (SD, 2.99), and the proportion of boys and girls
was 51.8% and 48.2%, respectively. In the present study population, more children lived in higher population density areas (65.3%).

### Table 1
Baseline demographics and exposure of air pollutants in Taiwan children, 2000–2012

| N = 244607 | n   | %  |
|------------|-----|----|
| Gender     |     |    |
| Boys       | 126734 | 51.8 |
| Girls      | 117873 | 48.2 |
| Age, years | mean, SD | 6.09 | 2.99 |
| Urbanization level | 1 (highest) | 81894 | 33.5 |
|             | 2     | 77950 | 31.9 |
|             | 3     | 46364 | 19.0 |
|             | 4 (lowest) | 38399 | 15.7 |
| Exposure of air pollutants |     |     |
| PM<sub>2.5</sub> level (daily average, µg/m³) | mean, SD | 36.8 | 8.16 |
| Outcome    |     |     |
| Systemic lupus erythematosus | Yes | 394 | 0.16 |
| Follow-up time, years | mean, SD | 11.2 | 2.32 |

The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

PM, particulate matter; PM<sub>2.5</sub>, particles with aerodynamic diameter < 2.5 µm; THC, total hydrocarbons; SD, standard deviation

According to the location of the Taiwan air quality monitoring station, we collected the data of participants without SLE history under variable levels of PM2.5. We categorized the concentrations of each air pollutant into 4 levels based on quartiles, ranging from Q1 (the lowest concentration) to Q4 (the highest concentration). Children with higher exposure concentrations (Q3 and Q4) of PM2.5, lived in suburban areas, while those with lower exposure concentrations (Q1 and Q2) lived in the highest urbanization areas (Table 2).
### Table 2
Baseline urbanization level among quartiles of daily average concentration of particulate matter (PM2.5) in Taiwan children, 2000–2012

| Air pollutant Concentration | Quartile 1 (Q1) (lowest) | Quartile 2 (Q2) | Quartile 3 (Q3) | Quartile 4 (Q4) (highest) | *p*-value |
|-----------------------------|--------------------------|-----------------|-----------------|---------------------------|-----------|
| N = 244607                  | n (%)                    | n (%)           | n (%)           | n (%)                     | < 0.001   |
| Urbanization level          |                          |                 |                 |                           |           |
| 1 (highest)                 | 19547 (46.2)             | 24598 (41.7)    | 21523 (28.7)    | 16226 (23.8)              |           |
| 2                           | 7586 (17.9)              | 16989 (28.8)    | 27379 (36.5)    | 25996 (38.1)              |           |
| 3                           | 6889 (16.3)              | 9828 (28.8)     | 11993 (16.0)    | 17654 (25.9)              |           |
| 4 (lowest)                  | 8301 (19.6)              | 7644 (12.9)     | 14106 (18.8)    | 8348 (12.2)               |           |

*Chi-square test

The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

The daily average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

The incidence rate for SLE increased with PM2.5 exposure concentration, from 4.7 (Q1) to 21.9 (Q4) per 100,000 person-years (Table 3). The Kaplan-Meier plots (Fig. 1) with PM2.5 concentration stratified by quartile showed that patients exposed to higher PM2.5 concentrations had a higher accumulative incidence of SLE than did those exposed to lower PM2.5 concentrations during the 12-year observation period. In the multivariable Cox proportional hazard regression, the adjusted HR for SLE increased with the PM2.5 exposure concentrations from 2.74 to 4.23 compared with that for those exposed to the corresponding concentrations in the Q1 level (Table 3).
Table 3
The risk of systemic lupus erythematosus in children exposed to particulate matter (PM2.5) stratified by quartile of daily average concentration in Cox proportional hazard regression

|               | IR  | cHR | (95%CI)          | aHR† | (95%CI)          |
|---------------|-----|-----|------------------|------|------------------|
| 1st Quartile  | 4.7 | Reference group | Reference group |      |                  |
| 2nd Quartile  | 14.1| 2.97 | (1.88, 4.69)*   | 2.74 | (1.74, 4.33)*   |
| 3rd Quartile  | 13.5| 2.86 | (1.82, 4.47)*   | 2.65 | (1.69, 4.15)*   |
| 4th Quartile  | 21.9| 4.61 | (2.98, 7.13)*   | 4.23 | (2.74, 6.55)*   |

IR, incidence rate (per 100,000 person-years)
cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval

The daily average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

†Adjusted HR, adjusted for age, sex, monthly income, and urbanization level

* p < 0.001

Discussion
This is the first large population study to evaluate the exposure of ambient PM2.5 and the occurrence of cSLE over a long period of time. This longitudinal study showed that higher PM2.5 exposure concentrations increased the incidence rate of cSLE in Taiwanese children and suggests that ambient PM2.5 exposures may be a trigger for the development of cSLE.

Seventy years ago, the historic smog disaster, the 1948 Donora smog, killed 20 people and caused respiratory problems for 6,000 out of the 14,000 people living in Donora. [9] Since then, interest has increased regarding the harmful effects of air pollution. In 1963, the Clean Air Act was established and was last amended in 1990; it requires the Environmental Protection Agency (EPA) to set National Ambient Air Quality Standards (NAAQS) for pollutants considered harmful to public health and the environment. [10] The World Health Organization (WHO) also challenged governments around the world to improve air quality in their cities to protect peoples’ health. [11] However, from the report of WHO, there are still approximately 4.2 million deaths resulting from exposure to ambient air pollution and an additional 3.8 million deaths resulting from exposure to household air pollution, every year. Moreover, several model projections indicate that the contribution of outdoor air pollution to premature mortality could double by 2050. [4]

Air pollutants can be found anywhere in the air, both outdoors and indoors. Typically, the environment contains a mixture of gaseous and particulate pollutants. [12] Most air pollutants originate from human activities and emissions of ambient air pollution from regional sources may travel long distances across
national borders. [13] To protect air quality in the US, the EPA has mandated air quality standards called NAAQS for the following six air pollutants: ozone (O₃), lead (Pb), total suspended particulates (TSP) including PM2.5 and PM10, carbon monoxide (CO), sulfur dioxide (SO₂), and nitrogen oxides. These six air pollutants are called “criteria pollutants”. [14] An increasing number of epidemiological studies have demonstrated that exposure to air pollutants has harmful effects on cardiovascular and respiratory morbidity and mortality, particularly in children. [15–18] Children are known to have more adverse health effects to air pollution because of their higher minute ventilation, immature immune system, tendency to spend more time outdoors, and the continuing development of their lungs.[17–20]

PM 2.5 causes more of a burden than other air pollutants because these particles are composed of sulfates, metals, and other toxic substances that are adsorbed into their molecules. [19] The physical and chemical composition and size of airborne particulate matter vary widely with time and space. [20, 21] The airborne particulate matter originates from sources such as transportation-related emissions, road/soil dust, biomass burning, and agricultural activities which enter the atmosphere by anthropogenic and natural pathways. [22] PM 2.5 are more toxic because they can reach deeper areas of the respiratory tract and can be absorbed into the bloodstream, resulting in local and systemic inflammation. Exposed to excessive PM 2.5 results in numerous diseases such as asthma, chronic bronchitis, cancer, cardiovascular disease, diabetes, and premature death.[4, 23–26] For every 10 µg per cubic meter in PM 2.5, all-cause mortality increases by 7.3%. [27]

The associations between air pollution and immune-inflammatory responses have been noticed. Exposure to air pollution may cause major autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM). [28] Exposure to particulate matter (PM₁₀), sulfur dioxide, nitrogen dioxide (NO₂), ozone, and carbon monoxide was found to be associated with high disease activity in juvenile-onset SLE. [6] A recent Taiwanese study discovered a positive association of NO₂ exposure with the development of SLE in adults. [29] A recent Brazilian study revealed that exposure to inhalable fine particles increases airway inflammation and systemic inflammation in cSLE patients. Although the exact mode of onset and disease progression of SLE remains elusive, the urban-rural difference in prevalence, clustering of disease prevalence around polluted regions, and low concordance rates among monozygotic twins with SLE (around 24%) indicate that environment has a strong impact on SLE. [30] Experimental data strongly suggest that a complex interaction between the exposome (or environmental influences) and genome (genetic material) produce epigenetic changes (epigenome) that can alter the expression of genetic material and lead to the development of SLE in susceptible individuals. [30] Our study has some limitations. First, since air pollution is a dynamic mixture of different toxicants from natural and anthropogenic sources, including PM, O₃, CO, SO₂, nitrogen oxides (NOₓ), and so on, [17] monitoring the concentration of PM2.5 exposure does not fully eliminate the co-effects of mixed air pollutants. Second, since the monitoring stations are fixed outdoors, they may not reflect the true exposure level to air pollutants in patients. Third, since this is a retrospective study, we cannot control important confounders
such as genetic factors, family history of autoimmune disease, eating habits, leisure activity, sun protection habits, attitudes, body surface area, and cigarette smoking.

Conclusions

In conclusion, exposure to PM2.5 is a risk factor for developing cSLE. Although further studies are required to confirm these associations, our study suggests that awareness, education, and appropriate public policy for better air quality will result in a lower incidence of cSLE and will improve public health.

Abbreviations

fine particulate matter (PM2.5); childhood-onset systemic lupus erythematosus (cSLE); hazard ratios (HRs); particulate matters (PM); Taiwan National Health Insurance Research Database (NHIRD); International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM); Taiwan National Health Insurance (NHI); standard deviation (SD); The Taiwan Air Quality Monitoring Network (TAQMN); Taiwan Environmental Protection Administration (TEPA); Taiwan Air Quality-Monitoring Database (TAQMD); confidence intervals (CIs); Environmental Protection Agency (EPA); National Ambient Air Quality Standards (NAAQS); World Health Organization (WHO); ozone (O3); lead (Pb); carbon monoxide (CO); sulfur dioxide (SO2); systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); multiple sclerosis (MS); type 1 diabetes mellitus (T1DM); nitrogen dioxide (NO2); nitrogen oxides (NOx)

Declarations

Ethical Approval and Consent to participate:

The data were analyzed anonymously and informed consent is not applicable. This study has been approved by the Institute Review Board of China Medical University Hospital (CRREC-103-048) and complies with the principles outlined in the Helsinki Declaration.

Consent for publication:

This manuscript is an original article that has not been previously published and will not be submitted to any other journal. All the authors have read this manuscript and agree that the work is ready for submission, and accept responsibility for the manuscript's contents.

Availability of data and materials:

Data available on request due to privacy/ethical restrictions.

Competing interests:

None
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The authors have indicated they have no financial relationships relevant to this article to disclose.

Data sharing statement:

no additional data.

Authors' contributions:

Yen-Ju Shih, Lei Wan, and Chang-Ching Wei conceptualized and designed the study. Chen-Hao Mai and Yen-Ju Shih drafted the initial manuscript. Cheng-Li Lin carried out the initial analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Chang-Ching Wei coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Figures
Figure 1

Kaplan–Meier plot of incidence of Childhood-Onset Systemic Lupus Erythematosus (cumulative incidence rates) in patients with PM2.5 concentration stratified by quartile.