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Long-term exposure to traffic-related air pollution and systemic lupus erythematosus in Taiwan: A cohort study

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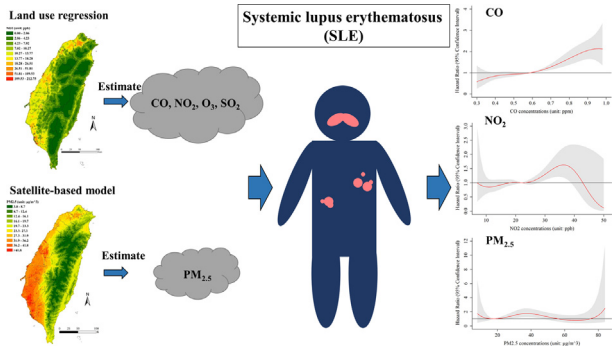
HIGHLIGHTS

- Only a few studies examine the effects of air pollution on SLE.
- A 1-km resolution hybrid satellite-based model and land use regression were used to estimate air pollutants' concentrations.
- There were positive associations of SLE with long-term exposure to CO, NO_2, and $PM_{2.5}$.
- In the exposure-response relationships, exposure to CO (>0.6 ppm), NO_2 (28–38 ppb), and $PM_{2.5}$ (18–46 μg/m^3) were associated with the increased risk of SLE.

GRAPHICAL ABSTRACT



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ABSTRACT

Systemic lupus erythematosus (SLE) is a multi-systemic chronic autoimmune disease, the etiology of SLE is still unclear. Only a few studies evaluated the associations between air pollution and SLE. We conducted a population-based cohort study in Taiwan to examine the associations of air pollution with SLE. A total of 682,208 individuals aged 18–70 years were retrieved from National Health Insurance Research Database. We applied 1-km resolution land use regression and satellite-based models to estimate air pollutant concentrations during 2001–2010. The mixed effect Cox models with time-dependent variables were performed to estimate the associations between air pollution and SLE, as hazard ratios (HRs) with 95% confidence interval (CI). We identified 1292 newly diagnosed SLE patients with average age of 43.26 ± 13.64 years, most of them were female. There were positive associations of SLE with exposure to a 9.76 ppb increase in nitrogen dioxide (NO_2), a 0.20 ppm increase in carbon monoxide (CO), and a 10.2 μg/m^3 increase in fine particles ($PM_{2.5}$) (HR = 1.21, 95% CI: 1.08–1.36, HR = 1.44, 95% CI: 1.31–1.59, and HR = 1.12, 95% CI: 1.02–1.23, respectively). Additionally, we observed negative associations with ozone (O_3) and sulfur dioxide (SO_2). According to the exposure-response relationships, exposure to NO_2 between 28 and 38 ppb, exposure to CO above 0.6 ppm, and exposure to $PM_{2.5}$ between 18 and 46 μg/m^3 were positively associated with SLE. The results suggested that long-term exposure to traffic-related gaseous air pollutants (NO_2 and CO) less than current National Ambient Air Quality Standards and $PM_{2.5}$ are significantly associated with the risk of SLE.

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1. Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic chronic autoimmune disease, and its etiology is still unclear. Previous studies have indicated that SLE may trigger by environmental factors (Barbhaiya and Costenbader, 2016). Air pollution has been demonstrated to induce systemic inflammatory responses (Törnqvist et al., 2007), which is speculated as a potential risk factor for development of autoimmune rheumatic disease (Sun et al., 2016).

Only a few epidemiological studies have assessed the associations between air pollution and SLE. Bernatsky and colleagues in Quebec, Canada recruited 237 SLE patients and reported significant positive associations between particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) and SLE activity (i.e., antibodies against double-stranded DNA and renal casts) (Bernatsky et al., 2011). Fernades and coworkers conducted a longitudinal panel study of repeated measures utilizing 409 consecutive medical visits in Sao Paulo, Brazil to evaluate the associations between short-term exposure to air pollution and juvenile-onset SLE. They found the positive significant associations of juvenile-onset SLE activity with an interquartile range (IQR) change of nitrogen dioxide (NO_2) at 13 days after exposure, an IQR change of carbon monoxide (CO) at 13 days after exposure, and an IQR change of particulate matter with an aerodynamic diameter <10 μm (PM_{10}) at 13 and 16 days after exposure, respectively (Fernandes et al., 2015). Based on the extent of clinicopathology, autoimmune diseases are classified into organic-specific and systemic with multi-organ involvement (Goldblatt and O'Neill, 2013; Kono and Theofilopoulos, 2013). In systemic autoimmune rheumatic diseases (SARDs), the regulation of immune system between invade pathogen recognition and self-recognition are impaired (Wahren-Herlenius and Dorner, 2013). SARDs is a group of systemic autoimmune diseases including SLE, Sjogren's Syndrome, scleroderma, polymyositis, dermatomyositis, or undifferentiated connective tissue disease (Kono and Theofilopoulos, 2013). There were two another studies have investigated the associations between SARDs and air pollution. Bernatsky and colleagues conducted an ecological study during 1993–2007 in Calgary city, Canada using land use regression (LUR) models to estimate long-term $PM_{2.5}$ and NO_2 concentrations. They analyzed the SARDs prevalence rates for each Calgary dissemination area (DA). A positive significant association between $PM_{2.5}$ and the risk of SARDs (odds ratio (OR) = 1.10, 95% CI 1.01–1.22) was observed when taking into accounts all Calgary subjects, but not for NO_2 (OR = 1.00, 95% CI 0.98–1.02) (Bernatsky et al., 2015). Additionally, the same study group carried out a population-based cross-sectional study in Alberta and Quebec, Canada using satellite-based remote sensing data to estimate $PM_{2.5}$ concentrations (2001–2006) for each DA in Alberta and each local social and health service center area (CLSC) in Quebec. They found OR of SARDs was increased with $PM_{2.5}$ levels in Alberta areas, (the OR of exposure to $PM_{2.5}$ level ≥ 8.12 μg/m^3 was 1.13, 95% CI 1.02–1.25 for non-first nations residents) and in Quebec areas (the OR of exposure to $PM_{2.5}$ level ≥ 11.81 μg/m^3 was 1.45, 95% CI 1.36–1.56) (Bernatsky et al., 2016). Overall, increased concentrations of $PM_{2.5}$ may be correlated with the increased risk of SARDs based on previous studies.

To our knowledge, the existed studies have rarely focused on the associations of SLE with long-term exposure to air pollution. Air pollution is a mixture of gases and particles, one of the main emission sources of air pollution in Taiwan is due to traffic. Traffic-related pollutants include gaseous species (carbon dioxide, CO, hydrocarbons, NO_x), and PM emitted from motor vehicles (HEI, 2010). In the study, we hypothesized that increased traffic-related gaseous air pollutants (i.e., CO, NO_2) and $PM_{2.5}$ concentrations may positively associate with the risk of SLE, we conducted a ten-years prospective cohort study to examine the hypothesis. Land use regression (LUR) models was used to estimate ground-level concentrations for traffic-related gaseous air pollutants (CO and NO_2), ozone (O_3), and sulfur dioxide (SO_2), and an advance satellite-based estimation model was applied to precisely estimate ground-level $PM_{2.5}$ in Taiwan.

2. Material and methods

2.1. Study population and design

Taiwan launched its National Health Insurance Program on March 1, 1995. The National Health Insurance Administration appointed the National Heath Research Institutes (NHRI) to publish the National Health Insurance Research Database (NHIRD) for research purpose since 2000. This population-based cohort study was based on a subset of NHIRD—the longitudinal health insurance database 2000 (LHID 2000). The LHID 2000 is a fixed cohort of one million individuals that were randomly selected from the registry of beneficiaries of the NHIRD in 2000. The LHID2000 is a representative group for the entire population of Taiwan in 2000 (Wang et al., 2018). The individuals in the LHID2000 were anonymous and de-identified to protect their privacy. The NHRI announced that there are no significant differences in sex distribution, age distribution, number of neonates every year, and amount of average insured payroll-related amount between the individuals in the LHID2000 and the NHIRD (NHRI, 2018). This study has been approved by the institute review board of China Medical University Hospital (CMU-REC-101-012), and it complied with the principles outlined in the Helsinki Declaration.

We retrieved participants aged18–70 years at the baseline (January 1, 2001) and followed up to the end of 2010 as study population. Participants met the following criteria were excluded from the study: individuals who received SLE diagnoses during January 1, 1996 to December 31, 2000 (n = 1152), who had missing information on sex (n = 418), missing information on the residential address (n = 43), and whose residential address located outside Taiwan main island and in the mountain area (n = 4004). Finally, this cohort comprises a total of 682,208 individuals.

2.2. Outcome of interest

The LHID2000 provides personal diagnostic information based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To ensure the accuracy of diagnoses, the National Health Insurance Administration appointed another independent team to examine and review a fixed proportion of the cases in the database (Lin et al., 2010). In this study, we selected individuals who received more than two consistent SLE diagnosis codes (ICD-9-CM code: 710.0) in outpatient visits or inpatient visits and defined incident SLE as individuals received the first diagnosis of SLE (Chan et al., 2016).

2.3. Exposure assessment

In this study, we leveraged LUR models to estimate ground-level concentrations of CO, NO_2, O_3, and SO_2. The LUR model is a high spatial resolution and cost-efficient method, which can capture variability of air pollution concentrations on intra-urban scale (Jerrett et al., 2005; Lee et al., 2015; Wu et al., 2017). The LUR models in this study were modified from the European Study of Cohorts for Air Pollution Effects (ESCAPE) modelling approach to estimate annual average air pollution concentration at 1-km spatial resolution (Beelen et al., 2013). The details of LUR models please refer to the supplementary materials. Additionally, in our previous work, we showed that satellite-based model is a reliable and validated method for estimating $PM_{2.5}$ concentrations in Taiwan (Jung et al., 2018). We modified the 10-km resolution model into a 1-km resolution model that incorporating the Multi-Angle Implementation of Atmospheric Correction (MAIAC) aerosol optical depth (AOD), meteorological variables, and land-use variables to estimate ground level $PM_{2.5}$ concentrations in this study. The details of the 1-km model have been described in the supplementary materials. We

calculated the annual average $PM_{2.5}$ by averaging the daily $PM_{2.5}$ estimates.

Then annual average concentrations of air pollutants, namely CO, NO_2, O_3, $PM_{2.5}$, and SO_2, were assigned to individuals according to their residential address in post-code level.

2.4. Covariates

The covariates include age, socioeconomic status (SES) and comorbidities. SES was derived by using the individual monthly insured payroll-related amount. We divided age and SES into four levels on the basis of quartiles (i.e., <25th percentile, 25th to 50th percentile, 50th to 75th percentile, and ≥75th percentile). The following comorbidities were treated as potential confounders in the relationships between air pollution and SLE: cerebrovascular disease (ICD-9-CM codes: 430–438), chronic kidney disease (CKD) (code: 585), coronary artery disease (codes: 410–414), diabetes mellitus (code: 250), hyperlipidemia (code: 272), hypertension (codes: 401–405), inflammatory bowel disease (IBD) (codes: 555, 556), and schizophrenia (code: 295) (Katsanos et al., 2012; Shen et al., 2014; Tiosano et al., 2017). Additionally, we used chronic obstructive pulmonary disease (COPD) diagnosis as surrogate for smoking.

Lupus nephritis is a manifestation of SLE and is a major risk factor for morbidity and mortality in SLE (Almaani et al., 2017). Thus, we retrieved lupus nephritis cases (ICD-9-CM code: 583.81) from our dataset for sensitivity analyses.

2.5. Statistical analysis

We used mixed effect Cox models incorporating time-dependent variables for annual mean concentrations of air pollutants and random effects for post-code level to evaluate the associations between annual average air pollutants and SLE (Kleinbaum and Klein, 2012; Therneau, 2018). To analyze time to diagnosis of SLE, each individual's follow-up time was censored at the year when the insurance was terminated, the person died due to another causes, or at the end of the follow-up period. For pollutants that were positively and significantly associated with SLE, we further employed the distributed lag nonlinear model (dlnm) (*dlnm* package in the R program) to explore exposure-response relationships between air pollutants and SLE. The functions of curve fitting for exposure-response relationships (b-spline or natural cubic, and degree of freedom from 4 to 9) were chosen based on the minimum Akaike information criterion (AIC). SLE is more frequent among females than among males, which has an overwhelming female to male ratio (Pons-Estel et al., 2010). To explore the potential effect modification in air pollution and SLE by sex, we introduced an interaction term between each air pollutant and sex (pollutant × sex) into the mixed effect Cox models to identify significant interactions between each air pollutant and sex. The effects of air pollutants on SLE were reported as hazard ratio (HR) with their 95% confidence interval (CI) per IQR (0.20 ppm) increase in CO level, per 9.76 ppb increase in NO_2, per 7.02 ppb increase in O_3 level, per 10.2 μg/m^3 increase in $PM_{2.5}$, and per 1.96 ppb increase in SO_2 level.

Air pollution is a complex mixture consisted of particles and gaseous pollutants. Based on the properties of air pollution, we then considered the associations between pollutants and SLE after adjusting for the second pollutant. We first fitted the single pollutant models, and then considered two pollutants models by fitting two air pollutants simultaneously in the same model. We did not include two pollutants that are highly correlated (if correlation coefficient >0.8) into the same model to exclude the potential collinearity problem. All statistical analyses were conducted in R program version 3.5.1 (Packages *coxme* and *dlnm*).

3. Results

3.1. Basic characteristics for study population

Table 1 showed the demographic characteristics of the study population. The mean age of subjects received the first SEL diagnosis was 43.26 ± 13.64years (range from 18.77 to 78.49– years). There were 1292 incident SLE cases within the study population of 682,208 subjects, and the incidence rate (IR) was 1.93 per 10,000 person-year (95% CI: 1.83–2.04). The female is more likely to develop SLE than male (HR = 6.34; 95% CI: 5.42–7.42). The low SES group (with monthly insured payroll-related amount below 1249 New Taiwan dollar (NTD)) have higher risk of SLE than other group (using SES < 1249 NTD as reference group, HR = 0.66, 95% CI: 0.56–0.78 for 1249 ≤ SES < 21,000 NTD; HR = 0.77, 95% CI: 0.67–0.90 for 21,000 ≤ SES < 31,800 NTD; HR = 0.75, 95% CI: 0.65–0.88 for SES ≥ 31,800 NTD). Moreover, comorbidities, namely cerebrovascular disease, CKD, COPD, coronary artery disease, hyperlipidemia, hypertension, and lupus nephritis are significantly and positively associated with SLE (Table 1).

3.2. Air pollution

The distributions of the annual average air pollutants' concentrations are shown in Table 2. There is a strong positive correlation between NO_2 and CO concentrations (correlation coefficient (r) = 0.87). This may reflect that the two pollutants have similar spatial distribution pattern in Taiwan (Fig. S2). The concentrations of NO_2 were moderately positively associated with SO_2 and $PM_{2.5}$ (r = 0.40 and r = 0.54, respectively). $PM_{2.5}$ concentrations were moderately correlated with SO_2 (r = 0.43). Additionally, the concentrations of O_3 were negatively correlated with CO and NO_2 (r = −0.47 and r = −0.36, respectively) (Table 3). This revealed that the spatial distribution of O_3 was distinct from those of CO and NO_2 (Fig. S2).

3.3. Air pollutants and systemic lupus erythematosus

According the results of single pollutant models, there were positive and statistical significant associations of SLE with exposure to an IQR increase (0.20 ppm) in CO concentrations (HR = 1.46, 95% CI: 1.33–1.61), an IQR increase (9.76 ppb) in NO_2 (HR = 1.24, 95% CI: 1.10–1.39), and an IQR increase (10.2 μg/m^3) in $PM_{2.5}$ (HR = 1.12, 95% CI: 1.02–1.23) (Table 4). The trends did not change substantially after adjusting for confounders, including age, sex, SES, cerebrovascular disease, CKD, COPD, coronary artery disease, hyperlipidemia, and hypertension (adjusted HR = 1.44, 95% CI: 1.31–1.59 for an IQR ppb increase in CO, adjusted HR = 1.21, 95% CI: 1.08–1.36 for an IQR increase in NO_2, and adjusted HR = 1.12, 95% CI: 1.02–1.23 for an IQR increase in $PM_{2.5}$, respectively) (Table 4). On the contrary, there were statistical significant and negative associations of SLE with O_3 and SO_2 (adjusted HR = 0.80, 95% CI: 0.73–0.89 for an IQR increase (7.02 ppb) in O_3 and adjusted HR = 0.83, 95% CI: 0.76–0.90 for an IQR increase (1.96 ppb) in SO_2, respectively) (Table 4). We did not observe any significant interactions between each air pollutant and sex (p-value = 0.75 for the interaction term between CO and sex; p-value = 0.96 for NO_2 and sex; p-value = 0.96 for O_3 and sex; p-value = 0.65 for $PM_{2.5}$ and sex; and p-value = 0.33 for SO_2 and sex). The associations of SLE with air pollution is the same strength in male and female group.

We further examined the exposure-response relationships of CO, NO_2, and $PM_{2.5}$ (Fig. 1). For the dlnm of CO, the best AIC was obtained with b-spline at the degree of freedom of 4 (minimum AIC = 39,526.95). The exposure-response relationship of CO showed that the HRs of SLE increased gradually between 0.60 and 0.90 ppm (HRs ranged from 1.02 to 2.06), and it reached a plateau at exposure to CO above 0.90 ppm (Fig. 1). For the dlnm of NO_2, the best AIC was obtained with b-spline at the degree of freedom of 5 (minimum AIC = 39,568.79). The exposure-response relationship of NO_2 is curvilinear,

Table 1
Descriptive statistics for basic characteristics of study population during 2001–2010.

	SLE cases (n = 1292)	Total (N = 682,208)	Person-year at risk	IR (95% CI) (per 10,000 person-years)	HRs (95%CI)
Sex					
Male	182	347,108	3,405,833.97	0.53 (0.46–0.61)	Reference
Female	1110	335,100	3,273,000.44	3.39 (3.19–3.59)	6.34 (5.42–7.42)
Age(year)					
<29	332	169,731	1,641,585.58	2.02 (1.80–2.24)	Reference
29 ≤ age < 38	307	171,357	1,669,174.15	1.84 (1.63–2.04)	0.91 (0.78–1.06)
38 ≤ age < 48	316	170,606	1,682,280.28	1.88 (1.67–2.09)	0.93 (0.80–1.08)
≥49	337	170,514	1,685,794.40	2.00 (1.79–2.21)	0.99 (0.85–1.15)
Socioeconomic status					
<1249	311	130,161	1,258,018.49	2.47 (2.20–2.75)	Reference
1249 ≤ SES < 21,000	284	179,202	1,732,676.08	1.64 (1.45–1.83)	0.66 (0.56–0.78)
21,000 ≤ SES < 31,800	383	202,042	2,004,906.00	1.91 (1.72–2.10)	0.77 (0.67–0.90)
≥31,800	314	170,803	1,683,233.85	1.87 (1.66–2.07)	0.75 (0.65–0.88)
Cerebrovascular accident					
No	1156	638,657	6,246,983.57	1.85 (1.74–1.96)	Reference
Yes	136	43,551	431,850.84	3.15 (2.625–3.68)	1.70 (1.43–2.03)
Chromic kidney disease					
No	1232	671,017	6,568,006.51	1.88 (1.77–1.98)	Reference
Yes	60	11,191	110,827.90	5.41 (4.04–6.78)	2.89 (2.23–3.74)
Chronic obstructive pulmonary disease					
No	874	559,147	5,459,139.01	1.60 (1.49–1.71)	Reference
Yes	418	123,061	1,219,695.40	3.43 (3.10–3.76)	2.14 (1.91–2.41)
Coronary artery disease					
No	1098	611,150	5,973,861.87	1.84 (1.73–1.95)	Reference
Yes	194	71,058	704,972.54	2.75 (2.36–3.14)	1.50 (1.27–1.74)
Diabetes					
No	1113	600,589	5,868,752.18	1.90 (1.79–2.01)	Reference
Yes	179	81,619	810,082.23	2.21 (1.89–2.53)	1.17 (1.00–1.36)
Hyperlipidemia					
No	991	555,232	5,419,016.70	1.83 (1.71–1.94)	Reference
Yes	301	126,976	1,259,817.71	2.39 (2.12–2.66)	1.31 (1.15–1.49)
Hypertension					
No	920	525,859	5,127,303.45	1.79 (1.68–1.91)	Reference
Yes	372	156,349	1,551,530.96	2.40 (2.15–2.64)	1.34 (1.19–1.51)
Inflammatory bowel disease					
No	1263	668,747	6,545,199.01	1.93 (1.82–2.04)	Reference
Yes	29	13,461	133,635.40	2.17 (1.38–2.96)	1.13 (0.78–1.63)
Schizophrenia					
No	1279	675,780	6,615,082.63	1.93 (1.83–2.04)	Reference
Yes	13	6428	63,751.78	2.04 (0.93–3.15)	1.06 (0.61–1.82)
Lupus nephritis					
No	1250	680,871	6,665,879.30	1.88 (1.77–1.98)	Reference
Yes	42	1337	12,955.11	32.42 (22.61–42.22)	17.31 (12.73–23.54)

Notes: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

which showed an inverted J-shape. The HRs of SLE were statistical significant and positive at exposure to NO_2 between 28 and 38 ppb, the maximum HR of SLE occurred at NO_2 concentration of 36 ppb, and it continuously decreased and became non-significant at exposure to NO_2 above 39 ppb (Fig. 1). The dlnm of $PM_{2.5}$ revealed that the best AIC was obtained with b-spline at the degree of freedom of 4 (minimum AIC = 39,573.12). The HR of SLE were statistical significant and positive at exposure to $PM_{2.5}$ between 18 and 46 μg/m^3, while became non-significant at $PM_{2.5}$ above 47 μg/m^3. Overall, we did not observe clear exposure-response relationships of SLE with NO_2 and $PM_{2.5}$.

In the two pollutants model, the associations between SLE and CO remained significant positive after controlling for O_3, $PM_{2.5}$, and SO_2 (adjusted HR = 1.40, 95% CI: 1.25–1.56 for exposure to CO with O_3; adjusted HR = 1.47, 95% CI: 1.32–1.64 for exposure to CO with $PM_{2.5}$; and adjusted HR = 1.42, 95% CI: 1.30–1.56 for exposure to CO with SO_2) (Fig. 2). Similarly, there were significant positive associations between NO_2 and SLE after incorporating $PM_{2.5}$ and SO_2 into the same model (adjusted HR = 1.18, 95% CI: 1.04–1.34 for exposure to NO_2 with $PM_{2.5}$ and adjusted HR = 1.48, 95% CI: 1.31–1.68 for exposure to NO_2 with SO_2). However, the associations of SLE with NO_2 were attenuated to null after adjusting with O_3 (adjusted HR = 1.13, 95% CI: 1.00–1.28) (Fig. 2). Additionally, the associations of SLE with $PM_{2.5}$ reduced and became non-significant when adjusted for CO, NO_2, and O_3 in the same

Table 2
The distribution of air pollution concentrations during 2001–2010.

Pollution (unit)	Mean	SD	Median	Min	Max	Q1	Q3	IQR
CO (ppm)	0.59	0.14	0.58	0.28	0.99	0.48	0.68	0.20
NO_2 (ppb)	21.80	6.61	20.61	6.55	50.42	16.92	26.68	9.76
O_3 (ppb)	23.82	5.66	23.22	15.36	65.69	19.57	26.59	7.02
$PM_{2.5}$ (μg/m^3)	34.4	7.6	34.0	7.1	84.4	29.0	39.2	10.2
SO_2 (ppb)	5.84	1.96	5.73	1.54	19.95	4.68	6.63	1.96

Notes: CO, carbon monoxide; IQR, interquartile range; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particles with aerodynamic diameter <2.5 μm; SD, standard deviation; SO_2, sulfur dioxide.

Table 3
The Pearson correlation coefficients of yearly average air pollutants in Taiwan.

	Spearman correlation coefficients				
	CO	NO_2	O_3	$PM_{2.5}$	SO_2
CO	1	**0.87**	−0.47	0.39	0.25
NO_2		1	−0.36	0.40	0.54
O_3			1	−0.08	−0.01
$PM_{2.5}$				1	0.43
SO_2					1

Notes: CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; $PM_{2.5}$, particles with aerodynamic diameter <2.5 μm.
bold > 0.8.

Table 4
Hazard ratios and 95% confidence intervals (CIs) for newly diagnosed systemic lupus erythematosus (SLE) during 2001–2010.

	Crude HRs (95% CI)	Adjusted HRs (95% CI)[a]
CO (0.20 ppm)	1.46 (1.33–1.61)	1.44 (1.31–1.59)
NO_2 (9.76 ppb)	1.24 (1.10–1.39)	1.21 (1.08–1.36)
O_3 (7.02 ppb)	0.79 (0.71–0.87)	0.80 (0.73–0.89)
$PM_{2.5}$ (10.2 μg/m^3)	1.12 (1.02–1.23)	1.12 (1.02–1.23)
SO_2 (1.96 ppb)	0.82 (0.76–0.89)	0.83 (0.76–0.90)

CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; and SO_2, sulfur dioxide.
[a] Adjusted HRs were adjusted for age, sex, socioeconomic status, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension.

model. Notably the associations with $PM_{2.5}$ remained significantly positive when adjusted for SO_2 (adjusted HR = 1.24, 95% CI: 1.12–1.37). There were consistently negative associations of SLE with exposure to O_3 and SO_2 after adjusted for the second pollutant (Fig. 2). Overall, the associations of SLE with air pollutants did not change substantially after adjusting for the second pollutant (Fig. 2). For sensitivity analyses, we did not find the effect modification of lupus nephritis in the associations between air pollutants and SLE (p for interaction > 0.05) (Table S1).

4. Discussion

In this study, we applied the 1-km resolution LUR and an advanced satellite-based estimation model to estimate concentrations of air pollutants in Taiwan. We used the mixed effect Cox models with time-dependent variables to evaluate the associations between SLE and air pollutants. According to the results of single pollutant models, we

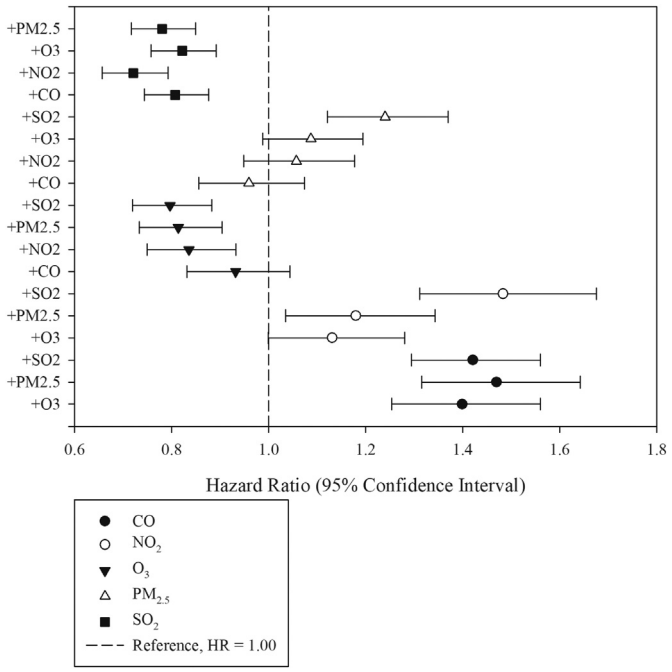

Fig. 2. The associations between air pollutants and systemic lupus erythematous (SLE) from two-pollutant model represented as hazard ratio with a 95% confidence interval. All models were adjusted for age, sex, socioeconomic status, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension. Carbon monoxide (CO; black circle); nitrogen dioxide (NO_2; hollow circle); ozone (O_3; black inverted triangle); particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$; hollow triangle); sulfur dioxide (SO_2; black square).

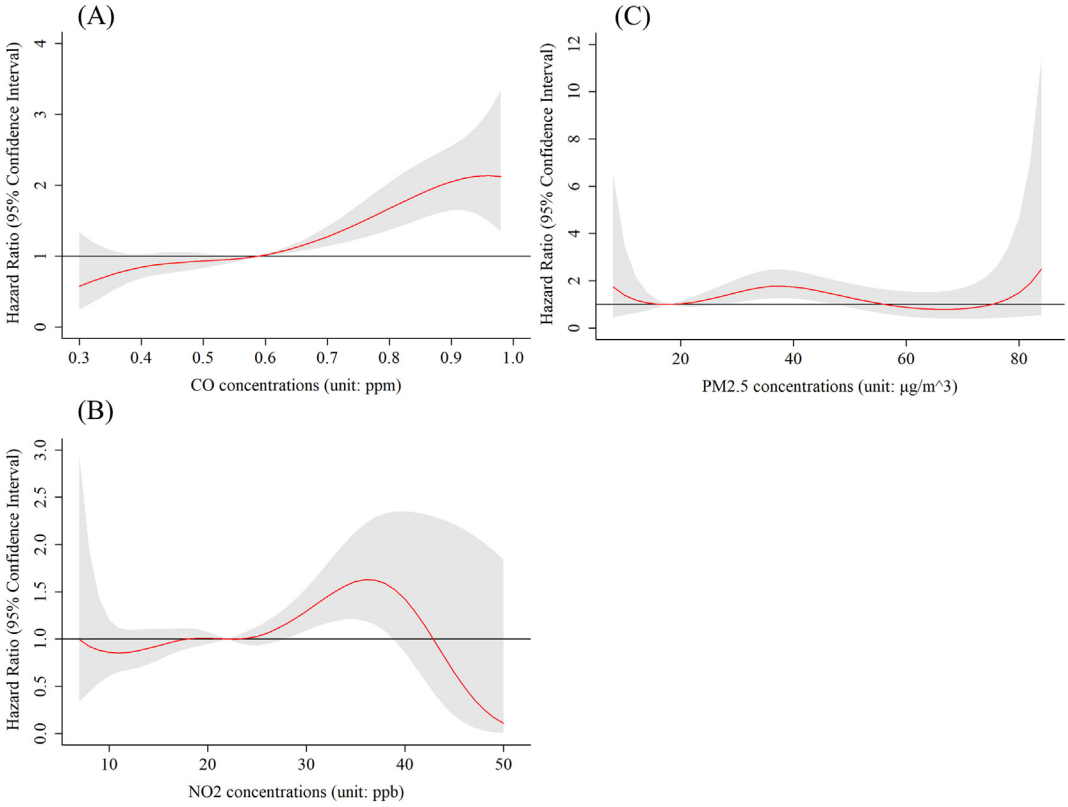

Fig. 1. Exposure-response relationships of carbon monoxide (CO; A), nitrogen dioxide (NO_2; B), and particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$; C) with systemic lupus erythematosus (SLE). The results were represented as hazard ratio with 95% confidence interval. The distribution lag non-linear models were adjusted for age, sex, socioeconomic status, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension.

found that exposure to increased traffic-related air gaseous pollutants (CO and NO_2) and $PM_{2.5}$ might be associated with the increased risk of SLE (Table 4). In contrast, exposure to increased O_3 and SO_2 were negatively associated with the increased risk of SLE. The associations of SLE with exposures to CO remained stable after considering with the second pollutant, while the associations of SLE with exposure to NO_2 were attenuated to null after adjusting with O_3. Additionally, the associations with $PM_{2.5}$ were reduced to null after controlling for CO, NO_2, and O_3, but remained significantly positive when adjusted for SO_2. According to the National Ambient Air Quality Standards (NAAQS) from US EPA, there is currently only standards for regulating 1-h and 8-h CO concentrations, while no standard for regulating annual mean CO (US EPA, 2018). We found that long-term exposure to CO above 0.6 ppm were associated with SLE by the exposure-response relationships of CO. Additionally, the NAAQS standards for annual mean NO_2 is 53 ppb (US EPA, 2018), we observed that even NO_2 concentrations less than current NAAQS standards (between 28 and 38 ppb) might still associate with SLE.

The biological mechanisms of the relationship between air pollution and SLE are still unclear. Several hypotheses have been postulated that air pollution may contribute to autoimmune diseases via oxidative stress, nitrosative stress, and systemic inflammation (Gawda et al., 2017; Ritz, 2010). Traffic-related air pollutants may cause oxidative stress and systemic inflammation (Laumbach and Kipen, 2010). The combination of CO with hemoglobin (Hb) to form carboxyhemoglobin (COHb) reduces the oxygen carrying capacity of the blood and causes tissue hypoxia (WHO, 2000). Hypoxia deprives usual supply of oxygen, and damage cells of the heart, muscle, brain and nervous system (Prockop and Chichkova, 2007; WHO, 2000). Moreover, chronic exposure to CO may induce oxidative stress by decreasing the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase and increasing the end-product of lipid peroxidation by reactive oxygen species (ROS) (Reboul et al., 2012). An in vitro study used normal human bronchial epithelial cells as model showing that exposure to NO_2 induced pro-inflammatory responses, and increased the generation of nitrate and interleukin (IL)-8 (Ayyagari et al., 2004). In human exposure chamber studies, exposure to NO_2 for four hours might induce neutrophilic inflammation in the bronchi of healthy humans (Blomberg et al., 1997). Repeated exposure of healthy human airways to 2 ppm NO_2 could trigger an upregulation of T helper (Th2) cytokines including IL-5, IL-10, IL-13 and intercellular adhesion molecule (ICAM)-1 in the bronchial epithelium (Pathmanathan et al., 2003). Higher cytokines expression (e.g., IL-6, IL-10) were observed in SLE patients, which may play an important role on pathogenesis of SLE (Blair et al., 2010; Gualtierotti et al., 2010). Furthermore, PM may induce oxidative stress via the adsorbed heavy metal on its surface, or PM may trigger the release reactive oxygen species (ROS) after phagocytosis by macrophage and lead to increase in oxidative stress (Mazzoli-Rocha et al., 2010). From the animal study, exposure to traffic-related PM pollutant enhanced the expression of inducible nitric oxide synthase (iNOS) (Bai et al., 2011). The overexpressed activity of iNOS may lead to exacerbated tissue damage in SLE (Oates and Gilkeson, 2006).

Getting clues from epidemiological studies that assessed the associations between air pollution and autoimmune rheumatic diseases. Hart and colleagues conducted a perspective cohort study in the U.S. finding that women living within 50 m of a major road had a 31% increased HR of rheumatoid arthritis (RA), while they did not examine associations of RA with specific air pollutants (Hart et al., 2009). Moreover, the same group performed case-control study in Sweden to examine the associations of RA with long-term exposure to air pollution, namely NO_2, PM_{10}, and SO_2 in the preceding 5 to 20 years before RA diagnosis. They found significant associations of RA with exposure to NO_2 in the preceding 5 and 10 years before RA diagnosis (OR = 1.19, 95% CI: 1.01–1.40 and OR = 1.22, 95% CI: 1.07–1.40, respectively) in anti-citrullinated protein antibody (ACPA)-negative phenotype group (Hart et al., 2013). In Taiwan, we have conducted a cohort study with more 0.3 million subjects and found that exposure to traffic-related air pollutants were significantly positively associated with RA diagnosis (adjusted HR = 1.17, 95% CI: 1.16–1.18 for a 100 ppb increase in CO and adjusted HR = 1.54, 95% CI: 1.45–1.64 for a 10 ppb increase in NO_2) (Jung et al., 2017b).

We observed consistent negative associations between O_3 and SLE (Table 4 and Fig. 2). In addition, it should be noted that the association between NO_2 and SLE were attenuated to null when controlling for O_3. The inverse relationship between the associations of health outcomes with NO_2 and O_3 was well-recognized in previous epidemiological studies that evaluated the effects of long-term NO_2 and O_3 (Atkinson et al., 2013, 2015; Coogan et al., 2017; Lee et al., 2016). This could be partially explained by inverse associations of O_3 with other pollutants ($r = -0.47$ for CO, $r = -0.36$ for NO_2, and $r = -0.08$ for $PM_{2.5}$). Based on our LUR model, the O_3 concentrations were negatively correlated with the axis corresponding to traffic-related area (PC1) and positively correlated with the axis corresponding to forest area (PC3) (Table S4). In contrast to O_3, the NO_2 concentrations were highly positively associated with the axis corresponding to traffic-related area (PC1) (Table S4). The spatial distribution of O_3 estimates from LUR model represented a distinct regional pattern comparing with NO_2 estimates (Fig. S2). This differences in regional pattern is likely to explain the observed inverse relationship between NO_2 and O_3. Furthermore, we could not rule out the possibility of measurement error form our LUR model for O_3, because leave-one-out cross validation (LOOCV) results showed that the performance of LUR for O_3 is not good enough (LOOCV $R^2 = 0.35$ with a root mean squared error (RMSE) of 3.53 ppb). The LUR may not adequately predict the spatial pattern of O_3, which is likely to result in the negative association between O_3 and SLE. Moreover, we also found negative associations between SO_2 and SLE (Table 4 and Fig. 2). A large proportion of sulfur oxides (SO_x) in Taiwan was emitted from coal-fired power plant, steel mill, and chemical materials manufacturing industry (36.43%, 11.82%, and 10.82%, respectively), but only a few from other types of industrial facilities, such as cement plant, textile industry, food manufacturing industry (TEPA, 2019). However, we could not discriminate the types of industrial facilities by using the land use variable, the areas of all types of industrial facilities were categorized to the same variable, the industrial area, in the LUR model. This may introduce the potential measurement error in this study. Although the performance of LUR for SO_2 is higher than the performance of inverse distance weighting (IDW) for SO_2 (CV $R^2 = 0.49$ with a RMSE of 1.48 ppb for LUR and CV $R^2 =$ for 0.35 with a RMSE of 2.41 ppb for IDW) (Jung et al., 2017a). Still, the performance of LUR model for SO_2 is not good enough as the performance for CO and NO_2 in Taiwan. Overall, our results related to the association of SLE with O_3 and SO_2 should be interpreted cautiously. The future study could seek for alternative models for these two pollutants.

This study has several strengths. Firstly, we use a large population-based prospective cohort to assess the relationships between air pollution and incident SLE. This study has strong generalizability and statistical power, and temporal issue could be eliminated. Secondly, LUR and satellite-based estimation model with higher spatial resolution were used to perform exposure assessment, which can take into accounts potential impacts of finer spatial variability of air pollutants. According to the cross validation results, the performances of LUR model for CO and NO_2, and satellite-based model for $PM_{2.5}$ are high (cross validation $R^2 = 0.60$, 0.72, and 0.78 for CO, NO_2, and $PM_{2.5}$, respectively, please refer to supplementary material Table S3). Our exposure assessment approaches can reduce misclassification bias and overestimation of exposure. Thirdly, mixed effect Cox models incorporated time-dependent variables were conducted to evaluate the associations of SLE with exposure to air pollution. This method considered the change of air pollutant concentrations over time, which allowed us to eliminate the potential bias (Kleinbaum and Klein, 2012).

There are also limitations should be noted. First, since some important confounders are unavailable from LHID2000 such as family history of SLE, genetic factors, personal behavior or habitat, and occupational

exposure (e.g., silica or solvents), we cannot rule out the possibilities that these confounders may influence our results. Second, we could not exclude the possible misclassification of SLE cases due to diagnosis by physicians. The errors in SLE classification are assumed to be non-differential in lower and higher exposure group. Nevertheless, our nationwide population from NHIRD have sufficient numbers of subjects, which could reduce the uncertainty due to random error that is typically presented in smaller sample size studies. Third, the follow-up time for each individual was set-up as censored at the year when insurance is terminated. This may result in misclassification for employees who change their jobs or end their employment. The National Health Insurance (NHI) in Taiwan is a single-payer compulsory and universal insurance program, and it covered nearly 99% of all residents by 2010 (Wu et al., 2010). Unemployed persons can still participate in the NHI under the district office, and the percentage of premium paid is relatively low. Although we could not rule out potential misclassification for these kinds of people, we think this kind of misclassification may not be an issue in the dataset.

5. Conclusions

In conclusion, our study evaluated the relations between exposure to air pollution and newly diagnosed SLE by applying LUR and an advanced satellite-based estimation model. We provide evidence that ambient air pollution may play an important role of SLE, the findings suggest that long-term exposure to CO and NO_2 concentrations less than existed NAAQS, and $PM_{2.5}$ are associated with an increased risk of SLE. Further research is needed to confirm these findings and evaluate potential biological mechanisms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.03.018.

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