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Air pollutants and development of interstitial lung disease in patients with connective tissue disease: a population-based case–control study in Taiwan

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ABSTRACT

Objective The aim of this study was to assess the association between air pollutant exposure and interstitial lung disease (ILD) in patients with connective tissue diseases (CTDs).

Setting A nationwide, population-based, matched case–control study in Taiwan.

Participants Using the 1997–2013 Taiwanese National Health Insurance Research Database, we identified patients with newly diagnosed CTD during 2001–2013, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis (DMtis)/polymyositis (PM) and primary Sjögren's syndrome (pSS).

Primary and secondary outcome measures Patients with newly diagnosed ILD during 2012–2013 were identified as ILD cases, and selected patients with CTD without ILD matching (1:4) the CTD cases for CTD diagnosis, age, gender, disease duration and year of ILD diagnosis date were identified as non-ILD controls. Data of hourly level of air pollutants 1 year before the index date were obtained from the Taiwan Environmental Protection Agency. The association between ILD and air pollutant exposure was evaluated using logistic regression analysis shown as adjusted ORs (aORs) with 95% CIs after adjusting for potential confounders.

Results We identified 505 newly diagnosed CTD-ILD patients, including 82 with SLE, 210 with RA, 47 with SSc, 44 with DMtis/PM and 122 with pSS. Ozone (O_3) exposure (per 10 ppb) was associated with a decreased ILD risk in patients with CTD (aOR, 0.51; 95% CI, 0.33 to 0.79) after adjusting for potential confounders.

Conclusions A previously unrecognised inverse correlation was found between O_3 exposure and ILD in patients with RA and SSc. Further studies are warranted to explore the underlying mechanisms.

BACKGROUND

Interstitial lung disease (ILD) is characterised by progressive inflammation and fibrosis, and accumulating evidence has demonstrated an association between exposure to air pollutants and the development and disease course of ILD.[1 2] Autoimmune rheumatic diseases show a strong correlated with ILD, including connective tissue disease-associated ILD (CTD-ILD) as

Strengths and limitations of this study

► This population-based study was conducted on a relatively large sample size, which can be generalised to the national level.
► The study used two nationwide databases to address the association between exposure to air pollutants and the development of interstitial lung disease in patients with connective tissue disease.
► The selection bias of the present population-based study using claim data is minimal.
► Given the nature of the secondary data, the analysis misses some crucial variables, such as disease activity and laboratory data.

well as interstitial pneumonia with autoimmune features; furthermore, the development of CTD-ILD has been reported to be an important cause of morbidity and mortality in patients with CTD.[3 4] A recent Taiwanese study reported that exposure to air pollutants, primarily nitrogen dioxide (NO_2), was associated with incident systemic lupus erythematosus (SLE).[5] Given that exposure to air pollutants has been implicated in ILD and CTD, there is a need to investigate the association between exposure to air pollutants and CTD-ILD.

Among the distinct air pollutants, ozone (O_3) is generated through chemical reactions, the so-called quenching reaction, among pollutants, primary oxides of nitrogen, in the presence of sunlight.[6] Exposure to O_3 was implicated with an increased Th2 response through enhancing the type 2 innate lymphoid cell (ILC)-associated pathway in airway cells, and Th1 response appears to be dominant in ILD.[7 8] Intriguingly, previous studies have reported a positive association between exposure to O_3 and the risk of acute exacerbation as well as poor pulmonary function in patients with idiopathic pulmonary fibrosis (IPF).[9 10] However, few studies have shown that O_3 exposure might have an inverse

correlation with incident ILDs, and the quenching effect as well as dysregulated T cell response by O_3 might possibly underlie this intriguing correlation.[2 11 12] The aforementioned evidence indicates the complex association between exposure to air pollutants, particularly O_3, and ILD. Moreover, evidence of the impacts of exposure to air pollutants on incident ILD in patients with CTD is still lacking. Therefore, there is a crucial need to address the impact of exposure to air pollutants on the development of ILD among patients with CTD. The Taiwanese National Health Insurance Research Database (NHIRD) has facilitated population-based epidemiological studies. Therefore, in the present study, we aimed to conduct a population-based case–control study to explore the association between ILD development and exposure to air pollutants in patients with CTDs, including SLE, rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis (DMtis)/polymyositis (PM) and primary Sjögren's syndrome (pSS), using the NHIRD.

METHODS
Informed consent was waived as all the data used for analyses were deidentified.

Study design
This research was a nationwide, population-based, matched case–control study.

Data source
Taiwan had launched a single-payer, compulsory National Health Insurance programme in 1995, with nationwide coverage of up to 99.6% of Taiwan's population in 2015.[13] The NHIRD contains all-inclusive claims data regarding the information on registration, demographic characteristics, residence, medication prescription, diagnosis, examinations, procedures, surgeries, medical expenditure, outpatient services, inpatient services and medication prescription. The NHIRD also registered all patients with major illnesses such as CTDs and malignancies in the catastrophic illness registry in case the catastrophic illness-related diagnoses were validated by two independent specialists through a detailed review of patients' original medical records. A catastrophic illness certificate is then issued to these patients, who are then exempt from expenses for medical services. In the present study, we used multiple files, including registration file, ambulatory file, inpatient file and catastrophic illness registry file, in the NHIRD from 1997 to 2013. The accuracy of the claims data from the NHIRD has been improved by regularly auditing the original medical records. The NHIRD was managed by the National Health Research Institute and was released for research purpose after the encryption of personal information.

Identification of patients with CTD from the entire population in Taiwan
We used the 1997–2013 NHIRD to identify patients with CTDs who were registered in the catastrophic

illness registry between 2001 and 2013 for newly diagnosed CTDs, including SLE (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 710.0), RA (ICD-9-CM codes 714.0 and 714.30–714.33), SSc (ICD-9-CM code 710.1), DMtis (ICD-9-CM code 710.3), PM (ICD-9-CM code 710.4) or pSS (ICD-9-CM code, 710.2). The date of CTD diagnosis was defined as the date of initial application for a catastrophic illness certificate for the corresponding CTD. From patients with CTD, we included those who did not have overlapping CTD diagnoses and those who did not have any ambulatory or inpatient visit with a diagnosis of ILD (ICD-9 code 515 and 516.36) or idiopathic interstitial pneumonia before the time of CTD diagnosis as the CTD cohort (figure 1).

Identification of ILD cases from the CTD cohort
We identified those who had a new diagnosis of ILD (ICD-9 code 515 and 516.36) after the CTD diagnosis date during 2012–2013 as ILD cases. The index date was defined as the date of first ambulatory or inpatient visit with a diagnosis of ILD.

Selection of matched non-ILD controls from the CTD cohort
From the CTD cohort, we randomly selected those who never had a diagnosis of ILD matching (1:4) the ILD cases for diagnosis of CTDs, sex, age (±4 years), disease duration (±4 years) and the year of index date as non-ILD controls.

Measurement of exposure to air pollutants
The hourly level of air pollutants across from 60 air quality monitoring stations were used to calculate the mean level of exposed air pollutants, including particulate matter <2.5 µm in size (PM2.5), particulate matter <10 µm in size (PM10), NO_2, carbon monoxide, sulphur dioxide (SO_2) and O_3, 1 year prior to the index date.[14] The ambient air pollutant concentrations at each residential location were estimated using a spatio-temporal model built via a deep-learning approach.[15] In brief, we used graph convolutional neural network to estimate the level of air pollutants at each residential locations, and the ambient level of air pollutants at 374 residential locations across Taiwan was estimated based on the data of three air quality monitoring stations near the location.

Potential confounders
The factors that may affect the association between exposure to air pollutants and incident ILD were taken into account as the confounder in the regression to estimate the impact of air pollutant on incident ILD in patients with CTD. Potential confounders that were adjusted for in the multivariable logistic regression model included age, gender, disease duration, Charlson Comorbidity Index (CCI) without the chronic pulmonary disease, diagnosis with chronic obstructive pulmonary disease (COPD)/asthma, use of biological disease-modifying antirheumatic drugs (bDMARDs), use of conventional synthetic DMARDs (csDMARDs), use of immunosuppressants,
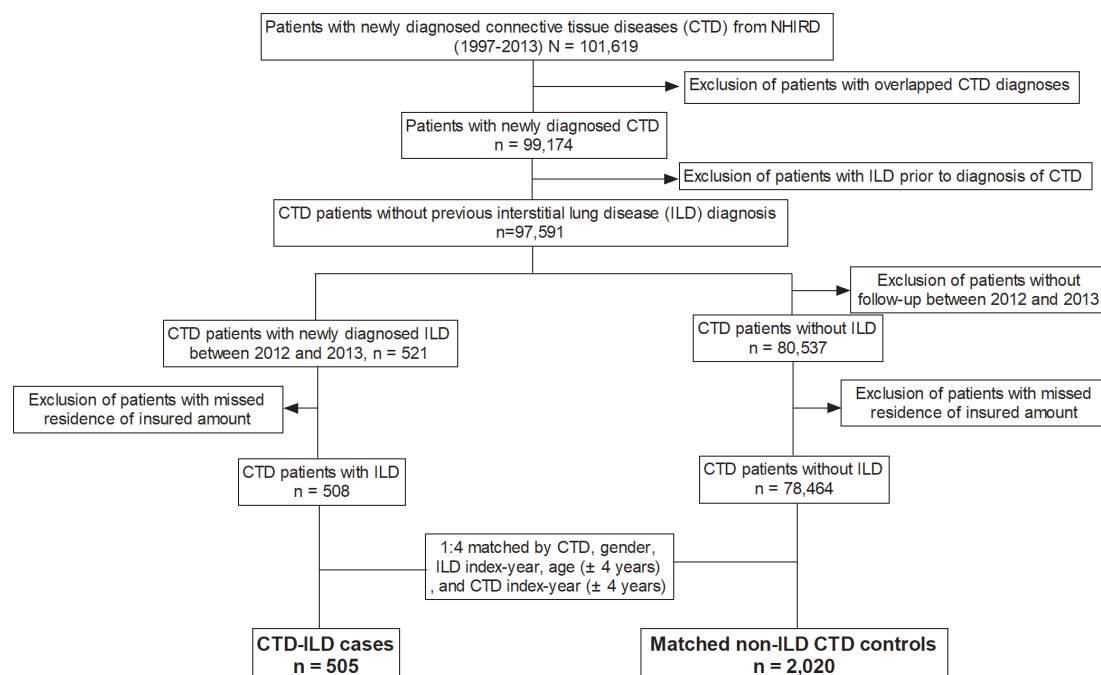
Figure 1 Flow chart of subject enrolment. NHIRD, National Health Insurance Research Database.

glucocorticoid (GC) dose (average daily prednisolone equivalent dose), urbanisation level of the patient's residence and the level of payroll-related insured amount. The presence of comorbidity was defined as the presence of one or more inpatient visits or at least three ambulatory visits with a corresponding ICD-9-CM code within 1 year before the index date. The CCI revised by Deyo *et al* was applied to analyse the general comorbid medical condition.[16] In Taiwan, the available bDMARDs before 31 December 2013 were anti-tumour necrosis factor (anti-TNF, including etanercept, adalimumab and golimumab), tocilizumab and rituximab. The csDMARDs included hydroxychloroquine (HCQ), sulfasalazine, methotrexate (MTX) and leflunomide (LEF). Immunosuppressants included cyclophosphamide (CP), ciclosporin (CSA), azathioprine (AZA) and mycophenolate mofetil/mycophenolic acid. Given that socioeconomic status might confound the association between air pollutant exposure and pulmonary diseases, we measured the socioeconomic status of each participant based on the urbanisation-level and payroll-related insured amount.[17] The urbanisation level of the patient's residence was categorised into four clusters based on population density (people/km^2), population ratio of elderly subjects aged >65 years, population ratio of subjects with educational levels of college or above, population ratio of agricultural workers and the number of physicians/100 000 subjects.[18] Payroll-related insured amount was transformed into categorical variable with four levels based on quantiles.

Statistical analyses

Data are represented as the number of patients (%) for categorical variables and either mean±SD for continuous variables. Categorical variables were compared using the χ^2 test or the Fisher's exact test, and continuous variables were compared using the t-test. Variables were considered as candidates for inclusion in the multivariable model if the associated univariate p value was lower than 0.20.[19]

The association between the risk of ILD development and the exposure to air pollutants was examined using a multivariable conditional logistic regression analysis after adjusting for age, gender, CCI, urbanisation level, level of payroll-related insured amount and medications for CTD and is represented as adjusted OR (aOR) with 95% CIs. All data were analysed using the statistical software V.9.3 (SAS Institute). A $p < 0.05$ was considered as statistically significant.

Patient and public involvement

This research was performed without patient involvement. Patients were not invited with regards to design of study, measurement of outcome and interpretation of results.

RESULTS
Study subjects with CTDs

A total of 505 patients with CTD-ILD were included in this study, consisting of 82 with SLE, 210 with RA, 47 with SSc, 44 with DMtis/PM and 122 with pSS. A total of 2020 patients were selected as matched non-ILD CTD controls. As shown in table 1, patients with CTD-ILD and the non-ILD CTD controls had similar distributions of age, gender and disease duration. Compared with the non-ILD controls, patients with ILD had a higher CCI (1.8±1.5 vs 1.4±1.4, p<0.01), were more likely to have COPD (25.0% vs 8.0%, p<0.01), received a higher dose of GC (5.1±8.5 vs 2.5±4.1 mg/day, prednisolone equivalent dose) and were more likely to use MTX (30.5% vs 22.4%, p<0.01), LEF (8.7% vs 5.1%, p<0.01), HCQ (61.0% vs 52.4%, p<0.01),

Table 1 Characteristics of enrolled subjects with ILDs and matched non-ILD controls

Variable	Non-ILD (n=2020)	ILD (n=505)	P value
Basic data			
Age, years	59.4±14.0	60.1±14.7	0.30
Gender, female	1520 (75.2)	380 (75.2)	1.00
Disease duration, years	6.9±5.1	6.7±5.7	0.45
CCI	1.4±1.4	1.8±1.5	<0.01
CCI without pulmonary disease	1.3±1.5	1.5±1.4	0.01
COPD	161 (8.0)	126 (25.0)	<0.01
Asthma	25 (1.2)	12 (2.4)	0.06
Urbanisation			
Level 1	588 (29.1)	165 (32.7)	0.48
Level 2	634 (31.4)	152 (30.1)	
Level 3	317 (15.7)	74 (14.7)	
Level 4	481 (23.8)	114 (22.6)	
Payroll-related insured amount, New Taiwan Dollars			
≤15 840	615 (30.4)	160 (31.7)	0.94
15 841–20 100	393 (19.5)	96 (19.0)	
20 100–27 600	523 (25.9)	126 (25.0)	
≥27 600	489 (24.2)	123 (24.4)	
Medication			
csDMARDs			
Methotrexate	452 (22.4)	154 (30.5)	<0.01
Sulfasalazine	369 (18.3)	105 (20.8)	0.19
Leflunomide	103 (5.1)	44 (8.7)	<0.01
Hydroxychloroquine	1058 (52.4)	308 (61.0)	<0.01
Ciclosporin	49 (2.4)	28 (5.5)	<0.01
Azathioprine	191 (9.5)	67 (13.3)	0.01
Cyclophosphamide	31 (1.5)	27 (5.3)	<0.01
Mycophenolate mofetil	20 (1.0)	6 (1.2)	0.69
Glucocorticoid	1284 (63.6)	408 (80.8)	<0.01
Prednisolone equivalent, mg/day*	2.5±4.1	5.1±8.5	<0.01
bDMARDs			
Anti-TNF	95 (4.7)	42 (8.3)	<0.01
Etanercept	57 (2.8)	25 (5.0)	0.02
Adalimumab	36 (1.8)	18 (3.6)	0.01
Golimumab	3 (0.1)	0 (0.0)	0.39
Tocilizumab	1 (0.05)	2 (0.4)	0.04
Rituximab	16 (0.8)	10 (2.0)	0.02
Air pollutant levels			
PM2.5 (µg/m^3)	3.1±0.7	3.0±0.6	<0.01
PM10 (µg/m^3)	5.4±1.2	5.1±1.1	<0.01
SO$_2$ (ppb)	0.4±0.1	0.3±0.1	<0.01
NO$_2$ (ppb)	1.8±0.6	1.8±0.5	0.71
CO (ppm)	0.5±0.2	0.6±0.2	0.42
O$_3$ (ppb)	2.8±0.3	2.7±0.3	<0.01

Data are presented as mean±SD and N (%).
*Prednisolone equivalent.
bDMARDs, biological disease-modifying antirheumatic drugs; CCI, Charlson Comorbidity Index; CO, carbon monoxide; COPD, chronic obstructive pulmonary access; csDMARDs, conventional synthetic DMARDs; ILD, interstitial lung disease; MPA, mycophenolic acid; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{10}$, particulate matter <10 µm; PM$_{2.5}$, particulate matter <2.5 µm; SO$_2$, sulphur dioxide; TNF, tumour necrosis factor.

CSA (5.5% vs 2.4%, p<0.01), AZA (13.3% vs 9.5%, p=0.01), CP (5.3% vs 1.5%, p<0.01) and anti-TNF (8.3% vs 4.7%, p<0.01). The socioeconomic status, including the urbanisation level and the level of payroll-related insured amount, tended to be similar between patients with ILD and the non-ILD controls. Regarding the exposure to air pollutants, patients with ILD had a slightly lower average exposure to PM2.5 (3.0±0.6 vs 3.1±0.7 µg/m^3, p<0.01), PM10 (5.1±1.1 vs 5.4±1.2 µg/m^3, p<0.01), SO$_2$ (0.3±0.1 vs 0.4±0.1 ppb, p<0.01) and O$_3$ (2.7±0.3 vs 2.8±0.3 ppb, p<0.01) (table 1). Altogether, these data showed that patients with CTD-ILD used a higher dose of GC; had greater proportions of using csDMARDs,

immunosuppressants and anti-TNF and were exposed to lower levels of air pollutants, primarily PM2.5, PM10, SO$_2$ and O$_3$, than the non-ILD controls (see details in online supplemental dataset).

Association of the risk of ILD development with comorbidity and socioeconomic status

As depicted in table 2, CCI without the pulmonary disease (aOR, 1.56; 95% CI 1.13 to 2.16) and COPD (aOR, 3.60; 95% CI 2.68 to 4.82) were significantly associated with a higher risk of developing ILD in patients with CTD. In subgroup analyses according to CTD, the positive association between COPD and ILD remained significant in

Table 2 Crude and adjusted ORs (aORs) for the association between ILD and variables in patients with CTD

	OR (95% CI)	aOR (95% CI)
Comorbidity		
CCI without pulmonary disease	2.04 (1.52 to 2.74)	1.56 (1.13 to 2.16)**
COPD	4.21 (3.19 to 5.55)	3.60 (2.68 to 4.82)**
Urbanisation		
Level 1	Reference	
Level 2	0.86 (0.67 to 1.09)	
Level 3	0.83 (0.61 to 1.13)	
Level 4	0.85 (0.65 to 1.10)	
Payroll-related insured amount, New Taiwan Dollars		
≤15 840	Reference	
15 841–20 100	0.94 (0.70 to 1.25)	
20 100–27 600	0.92 (0.71 to 1.21)	
≥27 600	0.96 (0.71 to 1.30)	
Medication		
Methotrexate	1.75 (1.35 to 2.25)	1.41 (1.06 to 1.89)*
Sulfalazine	1.22 (0.93 to 1.61)	0.84 (0.62 to 1.14)
Leflunomide	1.85 (1.26 to 2.72)	1.47 (0.96 to 2.25)
Hydroxychloroquine	1.47 (1.19 to 1.80)	1.18 (0.93 to 1.48)
Immunosuppressants	2.05 (1.55 to 2.70)	1.35 (0.99 to 1.85)
Steroid†, mg/day	1.12 (1.09 to 1.14)	1.09 (1.06 to 1.11)**
Anti-TNF	1.99 (1.33 to 2.99)	1.25 (0.79 to 1.97)
Tocilizumab	8.00 (0.73 to 88.23)	7.81 (0.56 to 109.85)
Rituximab	2.50 (1.14 to 5.51)	1.55 (0.64 to 3.74)
Air pollutants		
PM2.5 (per 10 µg/m^3)	0.67 (0.58 to 0.78)	0.72 (0.47 to 1.09)
PM10 (per 10 µg/m^3)	0.80 (0.74 to 0.88)	1.06 (0.83 to 1.37)
SO$_2$ (per 10 ppb)	0.19 (0.08 to 0.49)	0.40 (0.12 to 1.30)
NO$_2$ (per 10 ppb)	1.03 (0.87 to 1.23)	
CO (per 1 ppm)	1.19 (0.78 to 1.80)	
O$_3$ (per 10 ppb)	0.50 (0.35 to 0.71)	0.51 (0.33 to 0.79)**

*P<0.05, **p<0.001.
†Prednisolone equivalent.
CCI, Charlson comorbidity index; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; ILD, interstitial lung disease; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{10}$, particulate matter <10 µm; PM$_{2.5}$, particulate matter <2.5 µm; SO$_2$, sulphur dioxide; TNF, tumour necrosis factor.

Table 3 Crude and adjusted ORs (aORs) for the association between the risk of ILD development and variables in patients with rheumatoid arthritis

Variable	Univariable	Multivariable
	OR (95% CI)	aOR (95% CI)
Comorbidity		
CCI without pulmonary disease	3.49 (1.67 to 7.30)	1.70 (0.77 to 3.71)
COPD	2.94 (1.98 to 4.36)	2.35 (1.54 to 3.59)**
Urbanisation		
Level 1	Reference	
Level 2	1.06 (0.71 to 1.57)	
Level 3	0.87 (0.54 to 1.40)	
Level 4	0.88 (0.58 to 1.32)	
Payroll-related insured amount, New Taiwan Dollars		
≤15 840	Reference	
15 841–20 100	1.10 (0.72 to 1.68)	
20 100–27 600	0.88 (0.59 to 1.30)	
≥27 600	0.95 (0.57 to 1.57)	
Medication		
Methotrexate	1.66 (1.22 to 2.26)	1.28 (0.91 to 1.82)
Sulfasalazine	1.16 (0.86 to 1.58)	
Leflunomide	1.94 (1.30 to 2.91)	1.35 (0.85 to 2.15)
Hydroxychloroquine	1.73 (1.25 to 2.38)	1.36 (0.95 to 1.94)
Immunosuppressants	2.68 (1.60 to 4.50)	1.53 (0.86 to 2.73)
Steroid†(†), mg/day	1.15 (1.10 to 1.21)	1.11 (1.05 to 1.17)**
Anti-TNF	2.11 (1.39 to 3.21)	1.31 (0.82 to 2.09)
Tocilizumab	8.00 (0.73 to 88.23)	11.19 (0.75 to 166.66)
Rituximab	2.67 (1.20 to 5.94)	1.67 (0.69 to 4.02)
Air pollutants		
PM2.5 (per 10 µg/m^3)	0.77 (0.61 to 0.97)	0.97 (0.50 to 1.89)
PM10 (per 10 µg/m^3)	0.86 (0.76 to 0.97)	0.89 (0.62 to 1.29)
SO$_2$ (per 10 ppb)	0.52 (0.13 to 2.03)	
NO$_2$ (per 10 ppb)	0.98 (0.75 to 1.28)	
CO (per 1 ppm)	0.96 (0.48 to 1.92)	
O$_3$ (per 10 ppb)	0.70 (0.41 to 1.20)	0.69 (0.37 to 1.29)

***p<0.001.
†Prednisolone equivalent.
CCI, Charlson Comorbidity Index; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{10}$, particulate matter <10 µm; PM$_{2.5}$, particulate matter <2.5 µm; SO$_2$, sulphur dioxide; TNF, tumour necrosis factor.

patients with RA, SLE, pSS and DMtis/PM, but not in patients with SSc (tables 3–5).

Association between medications for CTD and the risk of ILD development

As shown in table 2, a positive association can be found between prednisolone equivalent dose (mg/day) and ILD risk (aOR 1.09, 95% CI, 1.06 to 1.11) in all patients with CTD. The positive association between GC dose and ILD risk remained statistically significant in all of the subgroups of CTD (tables 3–5). Regarding the

use of DMARDs, we observed a positive association of ILD risk with MTX use among all patients with CTD (table 2). However, subgroup analyses of CTD revealed that the positive association between MTX use and ILD risk remained statistically significant only in patients with DMtis/PM (tables 3–5).

Association between exposure to air pollutants and ILD development

We then evaluated the factors associated with ILD development in patients with various CTDs. Exposure to O$_3$

Table 4 Crude and adjusted ORs (aORs) for the association between the risk of ILD development and variables in patients with systemic lupus erythematosus and primary Sjögren's syndrome

Variable	Sytemic lupus erythematosus		Primary Sjögren's syndrome	
	Univariable	Multivariable	Univariable	Multivariable
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Comorbidity				
CCI without pulmonary disease	2.87 (0.86 to 9.65)	1.64 (0.40 to 6.66)	1.47 (0.98 to 2.22)	1.36 (0.87 to 2.14)
COPD	7.83 (3.54 to 17.29)	10.52 (3.97 to 27.89)**	7.14 (3.85 to 13.24)	5.99 (3.04 to 11.78)**
Urbanisation				
Level 1	Reference	Reference	Reference	
Level 2	0.51 (0.27 to 0.94)	0.69 (0.27 to 1.78)	0.81 (0.50 to 1.31)	
Level 3	0.59 (0.28 to 1.23)	0.79 (0.26 to 2.44)	1.24 (0.68 to 2.25)	
Level 4	0.74 (0.37 to 1.47)	1.81 (0.48 to 6.88)	0.90 (0.53 to 1.55)	
Payroll-related insured amount, New Taiwan Dollars				
≤15 840	Reference		Reference	
15 841–28 800	0.61 (0.26 to 1.39)		1.18 (0.66 to 2.10)	
28 801–45 800	0.93 (0.46 to 1.88)		1.02 (0.58 to 1.78)	
≥45 801	1.07 (0.52 to 2.20)		0.86 (0.46 to 1.59)	
Medication				
Methotrexate	0.69 (0.19 to 2.44)		0.81 (0.29 to 2.26)	
Sulfasalazine	3.04 (0.99 to 9.26)	3.19 (0.81 to 12.56)	0.96 (0.41 to 2.25)	
Leflunomide	<0.01 (<0.01–>99)		1.33 (0.14 to 12.82)	
Hydroxychloroquine	1.27 (0.75 to 2.13)		1.26 (0.82 to 1.95)	
Immunosuppressants	1.47 (0.89 to 2.45)	1.06 (0.55 to 2.05)	3.39 (1.62 to 7.07)	1.84 (0.78 to 4.34)
Steroid†, mg/day	1.09 (1.05 to 1.14)	1.09 (1.03 to 1.15)**	1.17 (1.09 to 1.25)	1.11 (1.03 to 1.18)**
Air pollutants				
PM2.5 (per 10 µg/m^3)	0.59 (0.41 to 0.86)	0.23 (0.07 to 0.73)*	0.61 (0.44 to 0.84)	0.73 (0.30 to 1.76)
PM10 (per 10 µg/m^3)	0.79 (0.64 to 0.98)	1.96 (0.98 to 3.89)	0.76 (0.63 to 0.91)	1.04 (0.61 to 1.75)
SO$_2$ (per 10 ppb)	0.13 (0.01 to 1.30)	0.41 (0.01 to 15.74)	0.08 (0.01 to 0.61)	0.10 (0.01 to 1.41)
NO$_2$ (per 10 ppb)	1.41 (0.93 to 2.15)	0.98 (0.15 to 6.57)	0.99 (0.70 to 1.40)	
CO (per 1 ppm)	2.45 (0.96 to 6.20)	0.94 (0.03 to 26.11)	1.34 (0.59 to 3.04)	
O$_3$ (per 10 ppb)	0.23 (0.09 to 0.58)	0.06 (0.01 to 0.43)**	0.65 (0.31 to 1.34)	

*p<0.05, **p<0.005.
†Prednisolone equivalent.
CCI, Charlson Comorbidity Index; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NA, not available; ; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{10}$, particulate matter <10 µm; PM$_{2.5}$, particulate matter <2.5 µm; SO$_2$, sulphur dioxide; TNF, tumour necrosis factor.

(aOR, 0.51; 95% CI, 0.33 to 0.79) was found to have an inverse association with the risk of ILD development after adjusting for potential confounders. As shown in tables 3–5, the subgroup analyses based on CTD revealed that the protective effect of O$_3$ against ILD risk was consistently present in patients with SLE, but did not reach statistical significance in patients with the other CTDs.

DISCUSSION

The association between O$_3$ exposure and ILD development currently remains elusive, and evidence regarding air pollutant exposure and CTD-ILD is extremely sparse despite the increasing awareness of CTD-ILD. In this population-based case–control study, we found that O$_3$ exposure was inversely associated with the development of ILD in patients with CTD after adjusting for potential confounders, including concomitant medications and socioeconomic status. The finding highlights the previously unrecognised association between exposure to air pollutants, particularly O$_3$, and the development of CTD-ILD.

Although there is increasing evidence to implicate exposure to air pollutants in the development of ILD, current evidence remains elusive due to the varied definition for

Table 5 Crude and adjusted ORs for the association between the risk of ILD development and variables in patients with systemic sclerosis and dermatomyositis/polymyositis

| | Systemic sclerosis | | Dermatomyositis/ polymyositis | |
| | Univariable | Multivariable | Univariable | Multivariable |
Variable	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Comorbidity				
CCI without pulmonary disease	0.39 (0.11 to 1.46)	5.51 (1.11 to 27.26)*	1.55 (0.68 to 3.54)	
COPD	0.80 (0.33 to 1.91)	2.80 (0.97 to 8.07)	4.19 (1.38 to 12.71)	6.73 (1.39 to 32.51)*
Urbanisation				
Level 1	Reference	Reference	Reference	
Level 2	1.02 (0.47 to 2.20)	1.53 (0.56 to 4.18)	0.90 (0.39 to 2.08)	
Level 3	0.39 (0.11 to 1.46)	0.73 (0.15 to 3.68)	0.74 (0.26 to 2.13)	
Level 4	0.80 (0.33 to 1.91)	1.97 (0.51 to 7.57)	0.84 (0.31 to 2.27)	
Payroll-related insured amount, New Taiwan Dollars				
≤15 840	Reference		Reference	Reference
15 841–28 800	1.01 (0.36 to 2.79)		0.36 (0.12 to 1.11)	0.39 (0.09 to 1.61)
28 801–45 800	1.19 (0.45 to 3.12)		0.66 (0.25 to 1.77)	0.32 (0.09 to 1.16)
≥45 801	1.14 (0.42 to 3.14)		0.74 (0.30 to 1.86)	0.24 (0.06 to 0.94)*
Medication				
Methotrexate	1.00 (0.24 to 4.11)		5.70 (2.74 to 11.88)	7.55 (2.77 to 20.62)**
Sulfasalazine	<0.01 <0.01->99)		12.00 (1.25 to 115.36)	2.31 (0.14 to 36.92)
Leflunomide	2.00 (0.18 to 22.06)		>99(<0.01->99)	
Hydroxychloroquine	0.87 (0.44 to 1.72)		2.21 (1.12 to 4.39)	0.95 (0.38 to 2.38)
Immunosuppressants	2.11 (1.01 to 4.44)	1.05 (0.40 to 2.74)	1.52 (0.79 to 2.95)	
Steroid†, mg/day	1.16 (1.07 to 1.25)	1.12 (1.02 to 1.23)*	1.07 (1.02 to 1.11)	1.06 (1.004 to 1.12)*
Air pollutants				
$PM_{2.5}$ (per 10 µg/m^3)	0.69 (0.41 to 1.18)	1.14 (0.27 to 4.73)	0.57 (0.34 to 0.95)	0.31 (0.05 to 1.80)
PM10 (per 10 µg/m^3)	0.77 (0.57 to 1.04)	0.91 (0.35 to 2.35)	0.72 (0.54 to 0.97)	1.34 (0.47 to 3.79)
SO_2 (per 10 ppb)	0.06 (0.00 to 2.27)	0.12 (<0.01 to 16.34)	0.07 (0.00 to 1.99)	2.82 (0.01 to 574.01)
NO_2 (per 10 ppb)	0.95 (0.53 to 1.70)		0.90 (0.50 to 1.62)	
CO (per 1 ppm)	0.96 (0.24 to 3.86)		0.51 (0.11 to 2.43)	
O_3 (per 10 ppb)	0.28 (0.08 to 1.02)	0.16 (0.02 to 1.30)	0.30 (0.08 to 1.11)	0.36 (0.06 to 2.40)

*p<0.05, **p<0.005.
†Prednisolone equivalent.
CCI, Charlson comorbidity index; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NA, not available; ; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter <10 µm; $PM_{2.5}$, particulate matter <2.5 µm; SO_2, sulphur dioxide; TNF, tumour necrosis factor.

ILDs and the distinct air pollutants.[20] Rice et al conducted a community-dwelling population-based study in Framingham and reported that higher long-term exposure to elemental carbon, an indicator of traffic pollution, was associated with the incidence and progression of interstitial lung abnormalities (ILAs); however, they found no association between average levels of PM2.5 and incident ILAs.[12] In detail, unlike the positive association found between elemental carbon (OR 1.27, 95% CI 1.04 to 1.55) as well as PM2.5 (OR 1.02, 95% CI 0.85 to 1.23) and ILAs, an inverse association was found between O_3 (OR 0.91, 95% CI 0.78 to 1.06) and ILAs. Similarly, Sack C et al investigated 2671 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) Lung study and reported that exposure to ambient NO_x was associated with a higher prevalence of ILAs, but the association was not found with exposure to PM2.5 and O_3.[2] Remarkably, consistent with our finding and the result of the study of Rice et al, there was a significant inverse association between exposure to O_3 and incident ILAs (OR 0.30, 95% CI 0.10 to 0.93) in never-smokers. Furthermore, one delicate Italian study also found the trend of the inverse association between O_3 exposure and the incidence rate of IPF.[11] These three studies and our findings in patients with CTDs found the consistent but previously unrecognised inverse association between exposure to O_3 and incident ILDs.

Studies have postulated that the quenching effect of O_3 could possibly be responsible for the inverse association between exposure to O_3 and incident ILDs.[2 12] In fact, ground-level O_3 is a secondary pollutant resulting from the photochemical reaction among traffic-related air pollutants, including NO_2 and volatile organic compounds.[6] A number of previous studies reported an inverse correlation between O_3 level and traffic-related air pollutants, including NO_2 and elemental carbon.[2 11 12] However, some studies have reported that exposure to O_3 and other air pollutants was positively associated with a deteriorated disease course in patients with ILD, including hospitalisation, poor lung function and exacerbation of ILD.[9 10 21] The aforementioned discordant findings with regard to the impact of O_3 exposure on ILDs reflect the complexity of ILD pathogenesis, which consists of initial insults resulting in the influx of inflammatory cells as well as alveolar epithelial damage and the subsequent deterioration caused by the recruitment and activation of pulmonary fibroblasts and myofibroblasts.[22] Therefore, we postulate that O_3 exposure may exert distinct effects, including the quenching effect, on the development and clinical deterioration of ILD and the present study further provides evidence regarding the impact of O_3 exposure on the development of CTD-ILD.

The pathogenesis of CTD-ILD has been increasingly investigated in recent years, and the balance among T cells, including ILCs, has been identified to play an important role in the pathogenesis of CTD-ILD.[23–25] Sendo *et al*, using Zym-treated SKG mice to simulate RA-ILD, observed an increase in pathogenic Th17 cells in the inflamed lung tissue of RA-ILD mice and that tofacitinib ameliorated the ILD.[26] In another recent study, which analysed the cytokine profiles of 40 patients with PM/DMtis-ILD, Th1 cells were found to play a key role in the pathogenesis of PM/DM-ILD.[27] Intriguingly, O_3 has been implicated in a high Th2 response in airway cells by enhancing the type 2 ILC-associated pathway.[7 28] Therefore, the O_3-associated expansion of the Th2 pathway through ILCs may at least partly explain the potential protective effects of O_3 on the development of ILD in patients with CTD by ameliorating Th17/Th1-associated signalling in the airway.

Intriguingly, smoking was reported to affect the association between O_3 exposure and pulmonary diseases, including ILDs.[2] Sack *et al* observed that O_3 exerted a protective role in incident ILAs in never-smokers (OR 0.30, 95% CI 0.10 to 0.93) among participants in the MESA Lung study, whereas O_3 tended to be a risk factor for ILAs in ever-smokers (OR 1.44, 95% CI 0.52 to 4.01).[2] Smoking status is not recorded in the NHIRD; however, the majority of enrolled patients with CTD were females (74.9%), and there is a marked low prevalence of tobacco use among females in Taiwan (2.6%). Thus, we believe that the magnitude of the protective effect of O_3 against the development of CTD-ILD might at least partly be attributed by the high proportion of females in the study population.[29]

There are some limitations in the present study. First, the NHIRD cannot provide laboratory data including titers of autoantibody; however, the medication data are comprehensive. In addition, the diagnoses of SLE, RA and SS were validated by at least two experienced and qualified rheumatologists by reviewing patients' medical charts, laboratory findings and images to issue a catastrophic illness certificate. Similarly, the accuracy of ILD in the claim is also a concern. One recently published study aimed to validate claims-based algorithms for identification of ILD in patients with RA found that the accuracy of RA-ILD was high if the diagnosis was made by specialists.[30] In the present study, we merely enrolled patients within the aforementioned catastrophic illness registry file. Therefore, the diagnoses of CTD and ILD were made by the rheumatologist, and the risk for misclassification should be at least partly mitigated. Second, the disease activity of CTD is not recorded, but we believe that we have adjusted for the essential CTD-associated medications, which were comprehensively in NHIRD. We believe the adjustment of medications should largely reflect the disease activity. Third, varied mechanisms may underlie distinct CTDs; however, patients with distinct CTDs might have similar profibrotic pathways in the development of ILD.[31] Fourth, given the case–control design we merely claim the association, instead of causal inference, between exposure to air pollutants and incident ILDs in patients with CTD. Furthermore, we have conducted further analyses using a longer period (2 years) of air pollutant exposure, and the results were consistent with the finding in the present study using 1 year exposure to air pollutants (online supplemental table 1).

In conclusion, exposure to air pollutants is increasingly found to be associated with the development of a number of pulmonary diseases, including ILDs.

Recent evidence has demonstrated that O_3 exposure appeared to have a negative association with the development of ILDs. In the present population-based case–control study, we found that exposure to O_3 was inversely associated with incident CTD-ILDs among patients with CTD in Taiwan. Further studies are warranted to validate these findings and explore the underlying mechanisms.

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Supplemental Table 1. Crude and adjusted odds ratios for the association between ILD and variables in patients with CTD

	OR (95% CI)	aOR (95% CI)
Comorbidity		
CCI without pulmonary disease	2.16 (1.42–3.30)	1.64 (1.03–2.62)
COPD	4.35 (2.92–6.48)	3.63 (2.38–5.54)
Urbanisation		
Level 1	Reference	
Level 2	0.89 (0.63–1.27)	
Level 3	0.80 (0.51–1.25)	
Level 4	0.88 (0.61–1.29)	
Payroll-related insured amount, NTD		
≤15,840	Reference	
15,841–20,100	1.15 (0.76–1.72)	
20,100–27,600	1.00 (0.69–1.46)	
≥27,600	0.94 (0.61–1.46)	
Medication		
Methotrexate	1.66 (1.17–2.37)	1.31 (0.87–1.96)
Sulphasalazine	1.31 (0.90–1.93)	0.86 (0.56–1.32)
Leflunomide	1.57 (0.91–2.71)	1.07 (0.57–1.99)
Hydroxychloroquine	1.59 (1.18–2.14)	1.31 (0.95–1.82)
Immunosuppressants	2.21 (1.50–3.27)	1.29 (0.83–2.01)
Steroid[*], mg/day	1.13 (1.09–1.17)	1.11 (1.06–1.15)
Anti-TNF	2.10 (1.21–3.64)	1.25 (0.79–1.97)
Tocilizumab	8.00 (0.73–88.23)	1.46 (0.78–2.71)
Rituximab	2.55 (0.99–6.57)	8.11 (0.55–120.18)
Air pollutants		
PM2.5 (per 10 $\mu g/m^3$)	0.71 (0.57–0.89)	0.71 (0.37–1.37)
PM10 (per 10 $\mu g/m^3$)	0.82 (0.73–0.93)	1.10 (0.75–1.63)
SO_2 (per 10 ppb)	0.27 (0.08–0.94)	0.52 (0.10–2.68)
NO_2 (per 10 ppb)	1.04 (0.81–1.32)	
CO (per 1 ppm)	1.25 (0.69–2.26)	
O_3 (per 10 ppb)	0.54 (0.32–0.91)	0.47 (0.25–0.89)

[*]Prednisolone equivalent. Abbreviations: ILD, interstitial lung disease; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; TNF, tumour necrosis factor; NA, not available; PM2.5, particulate matter <2.5 μm; PM10, particulate matter <10 μm; SO2, sulphur dioxide; NO2, nitrogen dioxide; CO, carbon monoxide; O3, ozone.