Ecotoxicology and Environmental Safety 287 (2024) 117289

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

# Ambient air pollution and hospital admission for interstitial lung diseases: A multicenter hospital-based case-crossover study

Yi Zheng [a,1], Jun Liu [b,1], Nongping Feng [c], Jing Wei [d], Xiaohong Jia [a], Lu Luo [a], Ruijun Xu [a], Chunxiang Shi [e], Rui Wang [f], Hong Sun [g,*], Yuewei Liu [a,**]

[a] Department of Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China
[b] Department of Pulmonary and Critical Care Medicine, Guangzhou First People's Hospital, Guangzhou, China
[c] Department of Non-Communicable Disease Prevention and Control, Shenzhen Longgang Center for Chronic Disease Control, Shenzhen, China
[d] Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD, USA
[e] Meteorological Data Laboratory, National Meteorological Information Center, Beijing, China
[f] Luohu District Chronic Disease Hospital, Shenzhen, China
[g] Department of Environment and Health, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China

ARTICLE INFO

Edited by Richard Handy

*Keywords:*
Air pollution
Nitrogen dioxide
Sulfur dioxide
Interstitial lung diseases

ABSTRACT

Interstitial lung diseases (ILDs) lead to increased morbidity and premature deaths, imposing a significant burden on public health worldwide. Recently, several studies have linked ambient air pollution with the acute exacerbation of certain ILDs, but the evidence remains limited and inconclusive. With a multicenter hospital-based case-crossover design, we investigated 9128 patients who resided in Jiangsu province, China, and were admitted for ILDs between 2019 and 2022. Residential exposure to particulate matter with an aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$), $PM_{10}$, sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), carbon monoxide (CO), and ozone ($O_3$) was assessed using our validated grid datasets. We fitted conditional logistic regression models to examine associations of exposure to air pollutants with ILD admission. A 10 μg/m$^3$ increment of exposure to $SO_2$ and $NO_2$ was positively associated with a 16.18 % (95 % confidence interval [CI]: 3.79 %, 30.03 %) and 4.06 % (0.75 %, 7.49 %) increase in odds of ILD admission, respectively. All these associations appeared to be linear and the association of $SO_2$ exposure was significantly stronger among older adults. We estimated that over 10 % of ILD admissions could be attributable to exposure to $SO_2$ and $NO_2$. This study provides compelling evidence on the association of exposure to ambient air pollutants (including $SO_2$ and $NO_2$) with an increased odds of ILD hospitalizations. Our findings indicate that $SO_2$ and $NO_2$ exposures can lead to the exacerbation of ILDs, especially in elderly, and that the disease burden is considerable.

## 1. Introduction

Interstitial lung diseases (ILDs) consist of a large group of diseases that cause scarring of the lung and often manifest as dyspnea and reduced exercise capacity (Wijsenbeek et al., 2022). ILDs can significantly reduce patients' life quality, lead to increased morbidity and premature deaths, and therefore impose a significant burden on both individuals and society (Hilberg et al., 2018; Kreuter et al., 2021). According to findings from the Global Burden of Disease (GBD) study, ILDs accounted for 188,222 deaths and contributed to 4,042,150 disability-adjusted life-years globally in 2021 (http://vizhub.healthdata.org/gbd-compare). Because the lung damage from ILDs is often irreversible and can get worse over time, it is crucial to explore strategies to prevent exacerbations during its management.

ILDs arise from a series of intricate and incompletely comprehended environmental (e.g. asbestos), lifestyle, autoimmune, and genetic factors (Mathai and Danoff, 2016; Motamedi et al., 2023; Wells and Denton, 2014). Recent studies have provided some supportive findings that the

* Correspondence to: Department of Environment and Health, Jiangsu Provincial Center for Disease Control and Prevention, 172 Jiangsu Road, Nanjing, Jiangsu 210009, China.
** Correspondence to: Department of Epidemiology, School of Public Health, Sun Yat-sen University, 74 Zhongshan Second Road, Guangzhou, Guangdong 510080, China.
*E-mail addresses:* hongsun@jscdc.cn (H. Sun), liuyuewei@mail.sysu.edu.cn (Y. Liu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ecoenv.2024.117289
Received 31 July 2024; Received in revised form 15 October 2024; Accepted 31 October 2024
Available online 9 November 2024

exacerbation of certain ILDs (e.g. idiopathic pulmonary fibrosis [IPF]) is related to exposure to air pollutants (Conti et al., 2018; Goobie et al., 2023). As a major environmental challenge, exposure to ambient air pollutants, including particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤ 10 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), carbon monoxide (CO), and ozone ($O_3$), is considered as a prominent health determinant adversely affecting health of the respiratory system (Liu et al., 2019b; Tran et al., 2023; Turner et al., 2023). Ambient air pollution is pervasive in urban regions and have been recognized as having detrimental effects on lung function (Guan et al., 2016; Viegi and Taborda-Barata, 2022). Given the irreversible and progressive nature of lung damage in ILD patients and the significant severity of these pollutants, it becomes imperative to elucidate the effect of exposure to these pollutants on ILD exacerbation.

Existing evidence is limited to IPF from two single-city time-series studies, and the findings were mixed and inconclusive. In 2020, a time-series study conducted in Santiago, Chile during 2001–2012 revealed that exposure to $PM_{10}$ and $NO_2$ was related with a higher risk of IPF hospitalization (Dales et al., 2020). Conversely, an ecological study in Beijing, China during 2013–2017 identified significant adverse effects of $SO_2$, $NO_2$, $O_3$, and $PM_{2.5}$ (Liang et al., 2022). More studies are clearly warranted to assess potential adverse effects of exposure to air pollutants on ILD exacerbation.

To fill this research gap, a multicenter hospital-based case-crossover study in China was conducted to comprehensively quantify the association of short-term exposure to air pollutants with ILD hospitalizations. Excess ILD admissions were further estimated based on established exposure-response relationships. To detect potentially vulnerable populations, we also conducted several stratified analyses.

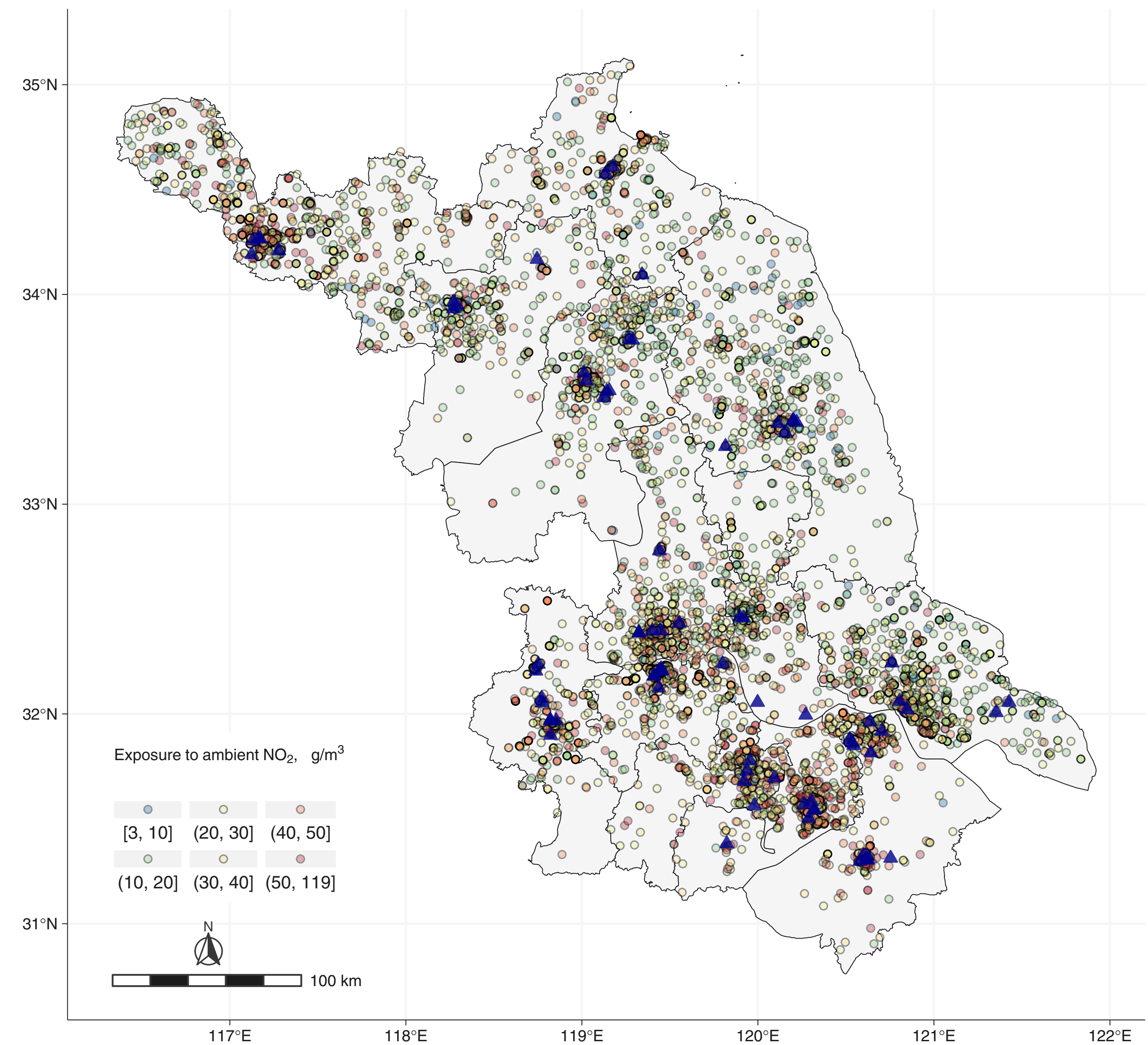


**Fig. 1. Spatial distribution of 79 hospitals (blue triangles) and study subjects (periods) in Jiangsu province, China during 2019–2022.** Definition of abbreviations: $NO_2$ = nitrogen dioxide. The color of periods presents $NO_2$ exposures, with red indicating higher concentrations and blue indicating lower concentrations.

## 2. Methods

### 2.1. Study subjects and outcome definition

ILD hospital admission data were acquired from 79 hospitals from January 2, 2019 to October 31, 2022, which provided healthcare services in each of the 13 prefecture-level cities in Jiangsu province, China (Fig. 1 and Fig. S1). The study period of ILD data varied across different hospitals, yielding a relatively smaller number of ILD admissions in 2022 (Fig. S2). We identified 9128 patients with ILDs (the 10th Revision of the International Classification of Diseases [ICD-10] codes: J84.0-J84.9) as the primary discharge diagnosis during the study period. The data analyses were based on each patient's first hospital admission due to ILDs. We collected demographic information (including age, sex, and residential address) and admission records (admission date) for each subject. The research protocol of this study was granted ethical approval from the Ethics Committee of the School of Public Health, Sun Yat-sen University, and there was no requirement for obtaining informed consent from the subjects.

### 2.2. Study design

A time-stratified case-crossover design was adopted to examine the effect of air pollution on ILD hospitalization. This design has been extensively applied to investigate the association of exposure to air pollutants and various health conditions (Di et al., 2017; Liu et al., 2019b). For each ILD patient, the day of admission was considered as the case day, whereas 3–4 control days were chosen by matching the same year, month, and weekday as the case day. For instance, if an ILD patient was admitted on a Friday in May 2021 (case day), we selected all other Fridays within May 2021 as the corresponding control days. According to this approach, each patient was treated as his or her own control, thereby enabling accounting for potential confounding factors such as time-invariant variables, long-term trends, and seasonality (Bateson and Schwartz, 1999).

### 2.3. Exposure assessment

Daily grid data on $PM_{2.5}$ (24-h mean concentration; spatial resolution: 1 km × 1 km), $PM_{10}$ (24-h mean concentration; 1 km × 1 km), $SO_2$ (24-h mean concentration; 1 km × 1 km), $NO_2$ (24-h mean concentration; 1 km × 1 km), CO (24-h mean concentration; 1 km × 1 km), and $O_3$ (daily peak 8-hour average concentration; 1 km × 1 km) in Jiangsu province from 2019 to 2022 were retrieved from our validated ChinaHighAirPollutant (CHAP) dataset (accessible at: https://weijing-rs.github.io/product.html). As a widely used air pollutant dataset with comprehensive coverage, high resolution, and exceptional quality, the CHAP dataset was generated using a comprehensive national ground-based observation network, extensive big data, and artificial intelligence techniques (Li et al., 2023). For $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, $O_3$, and CO, the corresponding cross-validated coefficient of determination was 0.92, 0.90, 0.84, 0.93, 0.92, and 0.80; the root-mean-square deviation was 10.8, 21.1, 10.1, 4.9, 13.5 μg/m$^3$, and 0.3 mg/m$^3$, respectively (Li et al., 2023; Wei et al., 2022a, 2021a, 2021b, 2022b).

To assess exposure to ambient air pollutants, a bilinear interpolation method was employed to extract daily concentrations at each ILD patient's geocoded residential address. As previous studies noted, the concentration of pollutants at the date of admission (lag 0), lag exposures for single days (lag 1 to lag 6: concentration on specific preceding day), and lag exposures for cumulative days (lag 01 to lag 06: average concentration of the current and preceding days) were used to assess the effect of exposure to air pollution on ILD hospitalization with consideration of lag effects (Liu et al., 2022).

### 2.4. Covariates

As suggested in previous studies, we considered weather conditions including daily 24-h average air temperature (℃) and relative humidity (%) as potential confounders in the model. We retrieved gridded weather conditions from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0; temporal resolution: 1 d; spatial resolution: 0.0625° × 0.0625°) (Liu et al., 2019a). Consistent with the exposure assessment on air pollution, we applied the bilinear interpolation method to obtain weather conditions at the geocoded residential addresses for each subject.

### 2.5. Statistical analyses

The Spearman's correlation coefficient was used to estimate correlations between air pollutants and weather conditions on lag 0 day. Using conditional logistic regression models with different lag periods, the percent change in odds (calculated as [odds ratio - 1] × 100 %) of ILD admission and its 95 % confidence interval (CI) for each 10 μg/m$^3$ increment of $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, $O_3$, and each 1 mg/m$^3$ of CO exposure was estimated to quantify the acute effects of these pollutants on ILD hospitalization. All models included both temperature and relative humidity at lag 03 day as natural cubic spline functions with 6 and 3 degrees of freedom (*df*), respectively (Xu et al., 2022b). To further explore the nonlinearity of exposure-response relationships, each pollutant was incorporated in the model with a natural cubic spline function with 3 *df*, and a likelihood ratio test was employed to examine if the association was nonlinear.

To evaluate the ILD burden due to ambient air pollution, we calculated the attributable fraction (AF) and attributable number (AN) of ILD admissions (Liu et al., 2022; Xu et al., 2022a). Based on the theoretical minimal risk exposure, the World Health Organization (WHO) air quality guidelines (AQGs), and the China's ambient air quality standards (GB 3095–2012 Grade II), we calculated the overall excess admissions and avoidable ILD admissions.

Stratification analyses were conducted by sex (male, female), age ($<$ 70 years, $\geq$ 70 years), and season (warm, cool) to identify susceptible populations. We further applied 2-sample $z$ tests to examine the differences in estimations of each stratum (Liu et al., 2019b; Xu et al., 2023). To assess the reliability of our models, 2-pollutant models were constructed by incorporating an additional pollutant into the same single-pollutant model. The likelihood ratio test was then used to compare the the two nested models (Xu et al., 2022b). R (version 4.3.2) was used for all analyses. A 2-sided $P < 0.05$ was considered as statistically significant.

## 3. Results

Table 1 provides a detailed description of the characteristics of the study subjects. During 2019–2022, we identified 9128 ILD admissions, yielding 9128 case days and 31,138 control days. Of these ILD patients, 42.1 % were female and the mean age was 67.4 years. As shown in Fig. S3, we identified that 31 patients (0.3 %) had alveolar and parietoalveolar conditions (J84.0), 2387 patients (26.2 %) had other ILDs with fibrosis (J84.1), 256 patients (2.8 %) had other specified ILDs (J84.8), and 6454 patients (70.7 %) were unspecified ILD (J84.9). On the date of admission, the mean concentration of $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, $O_3$, and CO were 38.3, 67.3, 9.3, 32.6, 112.5 μg/m$^3$, and 0.8 mg/m$^3$, respectively (Table 2). The Spearman's correlation coefficients demonstrated significant correlations between air pollutants and weather conditions (Fig. 2).

Fig. 3 and Table S1 illustrate percent changes in odds of ILD admission due to exposure to air pollutants across different lag periods. We identified significant associations of exposure to $SO_2$ and $NO_2$ with ILD admission. A 10 μg/m$^3$ increase of $SO_2$ exposure (lag 1 day) was significantly associated with a 16.18 % (95 % CI: 3.79 %, 30.03 %)

**Table 1**
Characteristics of the study population in Jiangsu province, China during 2019–2022.

| Characteristic | Value |
|---|---|
| ILD admissions, No. | 9128 |
| Case days, No. | 9128 |
| Control days, No. | 31,138 |
| Sex, No. (%) | |
| Female | 3840 (42.1) |
| Male | 5288 (57.9) |
| Age, yr | |
| Mean (SD) | 67.4 (13.6) |
| Median (IQR) | 69.0 (15.1) |
| No. (%) | |
| $< 60$ | 2095 (23.0) |
| 60–69 | 2557 (28.0) |
| 70–79 | 2949 (32.3) |
| $\geq 80$ | 1527 (16.7) |
| Season at admission*, No. (%) | |
| Warm | 3785 (41.5) |
| Cool | 5343 (58.5) |
| Year, No. (%) | |
| 2019 | 2774 (30.4) |
| 2020 | 2614 (28.6) |
| 2021 | 3405 (37.3) |
| 2022 | 335 (3.7) |

Definition of abbreviations: ILD = interstitial lung disease; SD = standardized deviation; IQR = interquartile range.
*Warm season was defined as May to September, while cool season was defined as October to April.

increase in odds of ILD admission. The estimates of risk for ILD admission associated with $NO_2$ ranged from 2.90 % (95% CI: 0.63 %, 5.23 %; lag 1 day) to 4.06% (95% CI: 0.75 %, 7.49 %; lag 04 day). These associations did not depart from linearity ($P_{nonlinear}$ for $SO_2$: 0.57; $P_{nonlinear}$ for $NO_2$: 0.64; Fig. S4). No significant associations were identified for PM, CO, or $O_3$ (all $P > 0.05$). The 2-pollutants analyses showed that these associations were generally stable (Table 3; all $P_{heterogeneity} > 0.05$).

According to the established exposure-response associations, we estimated that 10.4 % and 10.7 % of the ILD admissions were attributable to short-term exposure to $SO_2$ and $NO_2$ (Table 4). If the exposure to $NO_2$ was reduced to the 2021 WHO AQGs, 3.7 % of the ILD admissions can be avoidable, while few admissions can be avoidable for $SO_2$ exposures. Using the GB 3095–2012 Grade II levels, the avoidable AF was close to 0 for both $SO_2$ and $NO_2$.

With the exception of significantly stronger adverse effects of $SO_2$ exposure on ILD admissions among the elderly ($\geq$ 70 years), no effect modifications for sex, age, or season were identified in the stratified analyses (Table 5).

## 4. Discussion

We identified robust evidence of the linear association of both $SO_2$ and $NO_2$ with an increased odds of ILD admissions through a large multicenter hospital-based case-crossover study. In addition, adults over 70 years were more susceptible to $SO_2$ exposures. We estimated that more than 10 % of ILD admissions were attributable to ambient air pollution. Furthermore, our results indicated that the WHO AQGs and China's air quality standards may be insufficient in preventing hospital admission for ILDs.

Although previous studies have investigated the effects of air pollution on the hospitalization for specific ILDs such as IPF (J84.1), we are the first to explore the acute effects of air pollution on hospitalization for a broader category of ILDs (J84.0-J84.9) with a multicenter hospital-based case-crossover design (Rice et al., 2019; Sack et al., 2017). The findings illustrates that ILDs can be exacerbated by ambient air pollution, which is generally consistent with two recent time-series analyses. These two studies investigated the acute effects of air pollutant exposures on IPF admissions. However, the effects of specific pollutants were somewhat inconsistent with our results. The time-series analysis in Santiago, Chile concluded that exposure to $PM_{10}$ and $NO_2$ was positively associated with an increased risk of IPF hospitalizations (Dales et al., 2020), while the Beijing study highlighted the significant associations for $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$ (in men only), and $O_3$ exposure (Liang et al., 2022). In our study, we found consistent associations for both $SO_2$ and $NO_2$, and the corresponding disease burden was considerable, highlighting the need to pay close attention to $NO_2$ exposure when considering preventing ILD admissions. It should be noted that we used a case-crossover design with an individual-level exposure assessment, which is more accurate and may contribute to the inconsistent results. Other sources of inconsistency may include variations in study population, study period, and the exposure level.

The precise biological mechanisms underlying the adverse effects of $SO_2$ and $NO_2$ on ILD admissions remain to be elucidated; however, there are several plausible explanations, including the induction of epigenetic modifications, the upregulation of aberrant inflammatory, and profibrotic responses (Alfano et al., 2018; Guan et al., 2016). Many studies have demonstrated that $SO_2$ can elicit oxidative stress and induce the occurrence of apoptosis, leading to the hyperreactivity of airway epithelial cells and inflammatory response, which is closely associated with the pathogenesis of ILD (Meng et al., 2003; Reno et al., 2015; Wijsenbeek et al., 2022; Yun et al., 2011). Moreover, $SO_2$ triggers telomere attrition, impairs mitochondrial function, and therefore leads to oxidative stress, electron transport chain impairment, and oxidative phosphorylation damage to exacerbate ILD (Wang et al., 2023). Some studies found that $NO_2$ inhalation could trigger inflammatory response and compromise immune system by releasing pro-inflammatory mediators, including IL-8, TNF-α and IL-1β (Ayyagari et al., 2004; Hesterberg et al., 2009). In addition, exposure to $NO_2$ induces DNA methylation

**Table 2**
Distribution of exposure to ambient air pollutants and weather conditions on the date of hospital admission for ILDs in Jiangsu province, China during 2019–2022.

| Variable | Mean | SD | Min | $P_{25}$ | Median | $P_{75}$ | Max |
|---|---|---|---|---|---|---|---|
| Air pollutant | | | | | | | |
| $PM_{2.5}$, μg/m$^3$ | 38.3 | 24.6 | 3.3 | 21.5 | 31.6 | 47.9 | 211.2 |
| $PM_{10}$, μg/m$^3$ | 67.3 | 40.9 | 6.7 | 39.8 | 56.9 | 85.3 | 550.1 |
| $SO_2$, μg/m$^3$ | 9.3 | 3.4 | 2.4 | 6.9 | 8.5 | 10.8 | 35.0 |
| $NO_2$, μg/m$^3$ | 32.6 | 16.1 | 3.0 | 20.8 | 29.3 | 41.5 | 119.0 |
| CO, mg/m$^3$ | 0.8 | 0.2 | 0.3 | 0.6 | 0.7 | 0.9 | 2.6 |
| $O_3$, μg/m$^3$ | 112.5 | 47.0 | 4.0 | 76.7 | 106.0 | 141.2 | 305.6 |
| Weather condition | | | | | | | |
| Temperature, °C | 16.8 | 8.9 | −9.1 | 9.2 | 16.8 | 24.9 | 34.5 |
| Relative humidity, % | 74.4 | 13.0 | 26.1 | 66.2 | 75.9 | 84.4 | 96.2 |

Definition of abbreviations: ILD = interstitial lung disease; SD = standardized deviation; $P_{25}$ = the 25th percentile; $P_{75}$, the 75th percentile; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{10}$ = particulate matter with an aerodynamic diameter ≤ 10 μm; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide; CO = carbon monoxide; $O_3$ = ozone.

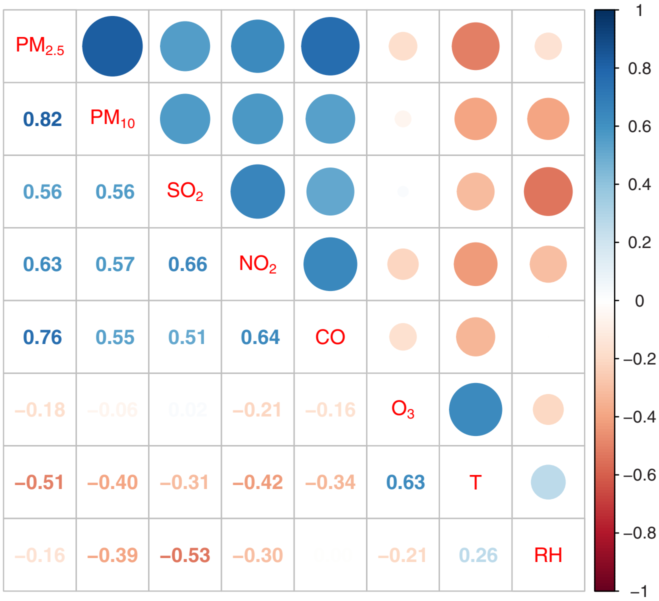


**Fig. 2. Spearman's correlation coefficients between air pollutants and weather conditions on the date of hospital admission for ILDs in Jiangsu province, China during 2019–2022.** Definition of abbreviations: ILD = interstitial lung disease; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{10}$ = particulate matter with an aerodynamic diameter ≤ 10 μm; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide; CO = carbon monoxide; $O_3$ = ozone; T = temperature; RH = relative humidity. The blue color indicates positive correlation coefficients, while red color represents negative correlation coefficients. The size of the dot presents the magnitude of the absolute value of correlation coefficient. All pairwise correlation coefficients were statistically significant ($P < 0.05$).

(DNAm) at the Forkhead box transcription factor 3 (FOXP3) gene locus, which is implicated in the pathogenesis of ILD (Goobie et al., 2020). Notably, aging exacerbates ILD progression through similar biological mechanisms as $SO_2$ exposure, which may help explain the susceptibility

**Table 3**
Estimated percent change in odds of ILD admission associated with exposure to each 10 μg/m$^3$ increase of exposure to $SO_2$ and $NO_2$ using single- and 2-pollutant models.

| Pollutant | $SO_2$ | | $NO_2$ | |
|---|---|---|---|---|
| | Percent change (95 % CI) | *P* for heterogeneity† | Percent change (95 % CI) | *P* for heterogeneity† |
| Single | 16.18 (3.79, 30.03) | | 4.06 (0.75, 7.49) | |
| 2-pollutant* | | | | |
| + $PM_{2.5}$ | 20.40 (5.73, 37.09) | 0.46 | 6.36 (2.03, 10.87) | 0.32 |
| + $PM_{10}$ | 21.53 (6.58, 38.57) | 0.53 | 6.29 (2.01, 10.76) | 0.42 |
| + $SO_2$ | | | 4.39 (−0.18, 9.17) | 0.80 |
| + $NO_2$ | 10.60 (−4.19, 27.67) | 0.67 | | |
| + CO | 22.48 (7.45, 39.60) | 0.42 | 6.35 (2.07, 10.81) | 0.06 |
| + $O_3$ | 19.99 (6.75, 34.86) | 0.19 | 4.68 (1.27, 8.20) | 0.24 |

Definition of abbreviations: ILD = interstitial lung disease; CI = confidence interval; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide.
*The adjusted pollutant was included as a natural cubic spline function ($df = 3$).
†*P* for heterogeneity was estimated using a likelihood ratio test.

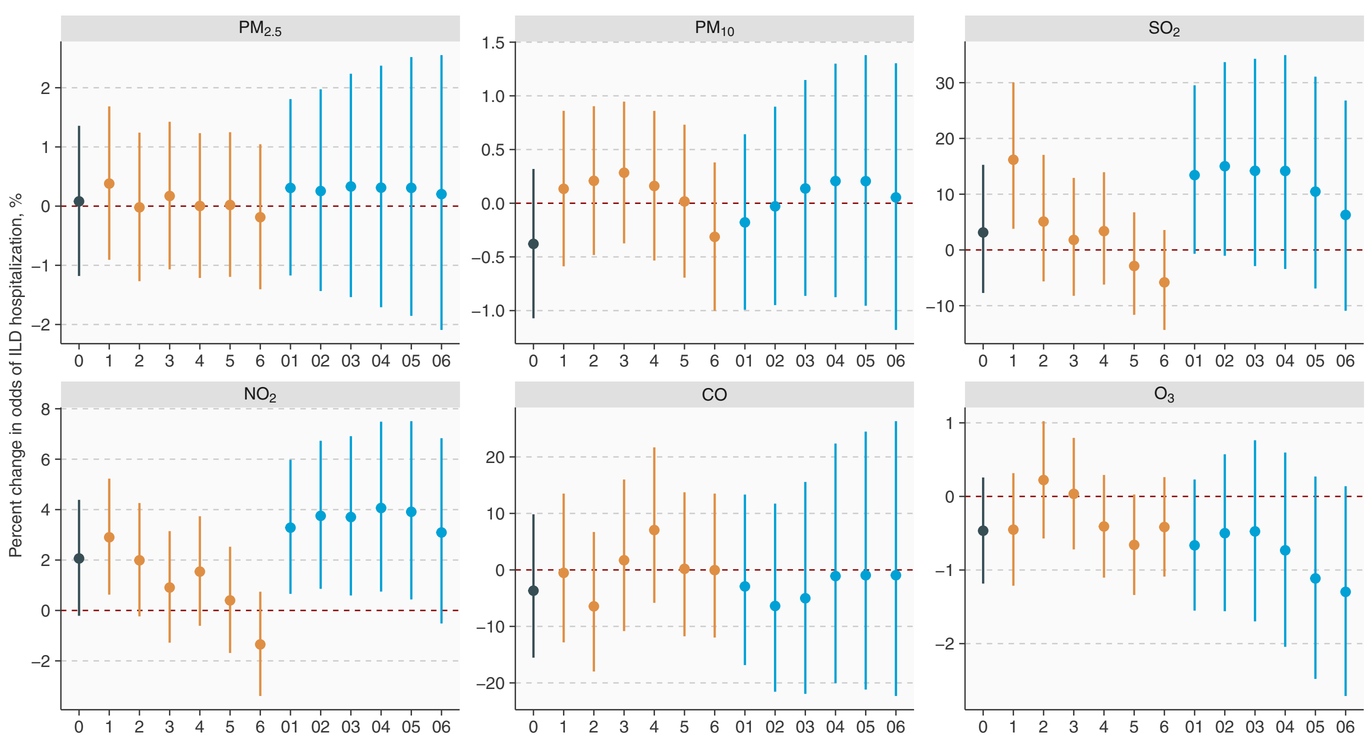


**Fig. 3. Estimated percent change in odds of hospital admission for ILDs associated with each 10 μg/m$^3$ increase of exposure to $PM_{2.5}$, $PM_{10}$, $SO_2$, $NO_2$, $O_3$, and each 1 mg/m$^3$ increase of exposure to CO.** Definition of abbreviations: ILD = interstitial lung disease; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{10}$ = particulate matter with an aerodynamic diameter ≤ 10 μm; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide; CO = carbon monoxide; $O_3$ = ozone.

**Table 4**
Excess admissions for ILDs attributable to short-term exposure to ambient $NO_2$ and $SO_2$.

| | Above Theoretical minimal risk exposure level* | Above 2021 WHO AQGs† | Above China standards‡ |
|---|---|---|---|
| AF (%; 95 % CI) | | | |
| $SO_2$ | 10.4 (2.7, 17.3) | < 0.1 | 0 |
| $NO_2$ | 10.7 (2.1, 18.4) | 3.7 (0.7, 6.5) | < 0.1 |
| AN (95 % CI) | | | |
| $SO_2$ | 948 (247, 1584) | < 1 | 0 |
| $NO_2$ | 976 (193, 1675) | 340 (66, 593) | < 1 |

Definition of abbreviations: ILD = interstitial lung disease; AQGs = air quality guidelines; AF = attributable fraction; AN = attributable number; CI = confidence interval; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide.
*The theoretical minimum risk exposure level for 24-h mean $SO_2$ and $NO_2$ concentration was 1.9 $\mu g/m^3$ and 3.8 $\mu g/m^3$, respectively.
†The 2021 WHO AQGs for 24-h mean $SO_2$ and $NO_2$ concentration was 40 $\mu g/m^3$ and 25 $\mu g/m^3$, respectively.
‡The Grade II value in ambient air quality standards in China (GB 3095–2012) for 24-h mean $SO_2$ and $NO_2$ concentration was 150 $\mu g/m^3$ and 80 $\mu g/m^3$, respectively.

**Table 5**
Estimated percent change in odds of ILD admission associated with each 10 $\mu g/m^3$ increase of exposure to $SO_2$ and $NO_2$ stratified by sex, age, and season*.

| Variable | $SO_2$ | | $NO_2$ | |
|---|---|---|---|---|
| | Percent change (95 % CI) | P value‡ | Percent change (95 % CI) | P value‡ |
| Sex | | | | |
| Male | 11.88 (−3.59, 29.84) | 0.44 | 4.06 (−0.24, 8.56) | 0.997 |
| Female | 22.41 (2.97, 45.52) | | 4.05 (−1.06, 9.43) | |
| Age | | | | |
| < 70 yr | 0.16 (−14.72, 17.64) | 0.01 | 3.17 (−1.45, 8.00) | 0.60 |
| ≥ 70 yr | 34.63 (14.96, 57.68) | | 4.95 (0.25, 9.87) | |
| Season† | | | | |
| Warm | 35.84 (5.32, 75.21) | 0.19 | 6.09 (−2.93, 15.95) | 0.55 |
| Cool | 12.18 (−1.13, 27.28) | | 3.03 (−0.53, 6.73) | |

Definition of abbreviations: ILD = interstitial lung disease; CI = confidence interval; $SO_2$ = sulfur dioxide; $NO_2$ = nitrogen dioxide.
*Percent changes and their 95 % CIs were estimated by conditional logistic regression models adjusting for air temperature and relative humidity.
†Warm season was defined as May to September, while cool season was defined as October to April.
‡*P* value < 0.05 indicates significant effect modification.

of older adults. Consistent with $SO_2$ exposure, aging can exacerbate the progression of ILDs by aggravating oxidative stress and mutating telomerase (Johannson et al., 2015; Meng et al., 2003; Sesé et al., 2018). In an animal study, antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione S-transferase in the lung increased with higher $SO_2$ exposure and greater age, indicating that both $SO_2$ exposure and aging imposed oxidative stress in the lung (Gümüşlü et al., 2001). Moreover, aging induces more cellular senescence and apoptosis, which can result in a higher level of inflammatory cytokines and therefore aggravate inflammation response caused by $SO_2$ exposure (Faner et al., 2012; Yun et al., 2011).

$NO_2$ and $SO_2$ have been recognized as a well traffic emissions tracer and a major pollutant from the burning of fossil fuels, respectively, and were both related to adverse health outcomes (Faustini et al., 2014; Orellano et al., 2021). Our study provides novel evidence that $NO_2$ and $SO_2$ can accelerate the deterioration of ILDs, emphasizing the importance of taking action to protect ILD patients and reducing exposure to air pollutants. Additionally, we estimated that the effects of $SO_2$ on ILD admission were more pronounced in older adults, and over 10 % of ILD admissions were attributable to $NO_2$ and $SO_2$. This further elucidates that mitigating exposure to air pollution may be useful for ILD patients especially in older individuals, and provides crucial evidence in preventing deterioration of ILDs for policy practitioners.

There are some strengths in our study. First, the population was from 79 hospitals in 13 cities in Jiangsu province, China, and the sample size was relatively large, which can help improve the representativeness of ILD patients and provide sufficient statistical power to detect potential associations. Second, the case-crossover design and our high-resolution air pollution data allowed us to conduct exposure assessment on ambient air pollution at an individual-level based on the geocoded residential address. The utilization of highly accurate evaluation can effectively reduce the exposure misclassifications and therefore lead to enhanced accuracy in estimating exposure-response relationships. Third, the time-stratified case-crossover design itself can mitigate potential confounding factors at individual-level, long-term trends, and seasonality.

There were also several limitations. First, even with the implementation of a case-crossover design to reduce the influence of time-invariant variables, long-term trends, seasonality, and adjustments made for meteorological conditions, it is essential to acknowledge the potential existence of residual or unmeasured confounders. Second, certain exposure misclassifications were inevitable due to lack of individual direct measurements of air pollution, though these misclassifications were approximately non-differential, and manipulated the results bias towards the null. Finally, it is imperative to be cautious when extrapolating our findings to diverse populations, given that the ILD patients included in our study were exclusively recruited from a single province.

## 5. Conclusion

Our study unveiled an association of short-term exposure to both $SO_2$ and $NO_2$ with an increased odds of ILD hospitalization, and that older adults were more susceptible to $SO_2$ exposures. Our study adds to the evidence that ambient air pollution contributes to ILD exacerbations, highlighting the urgency for implementing effective strategies to reduce exposure to air pollutants during the health management of ILD patients.

## Funding

This work was supported by the Key Project of Medical Science Research of Jiangsu Provincial Health Commission [grant number K2023045].

## CRediT authorship contribution statement

**Yi Zheng:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Jun Liu:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Nongping Feng:** Writing – review & editing. **Jing Wei:** Methodology, Data curation. **Chunxiang Shi:** Methodology, Data curation. **Rui Wang:** Writing – review & editing. **Hong Sun:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Yuewei Liu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Xiaohong Jia:** Writing – review & editing. **Lu Luo:** Writing – review & editing. **Ruijun Xu:** Writing – review & editing.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hong Sun and Yuewei Liu were supported by Jiangsu Provincial Health Commission. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.117289.

## Data Aavailability

The meteorological data can be accessed at http://data.cma.cn. The air pollution data can be obtained at https://weijing-rs.github.io. The mortality data are not publicly available.

## References


Alfano, R., Herceg, Z., Nawrot, T.S., Chadeau-Hyam, M., Ghantous, A., Plusquin, M., 2018. The impact of air pollution on our epigenome: how far is the evidence? (a systematic review). Curr. Environ. Health Rep. 5 (4), 544–578.

Ayyagari, V.N., Januszkiewicz, A., Nath, J., 2004. Pro-inflammatory responses of human bronchial epithelial cells to acute nitrogen dioxide exposure. Toxicology 197 (2), 149–164.

Bateson, T.F., Schwartz, J., 1999. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. Epidemiology 10 (5), 539–544.

Conti, S., Harari, S., Caminati, A., Zanobetti, A., Schwartz, J.D., Bertazzi, P.A., Cesana, G., Madotto, F., 2018. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. Eur. Respir. J. 51 (1), 1700397.

Dales, R., Blanco-Vidal, C., Cakmak, S., 2020. The association between air pollution and hospitalization of patients with idiopathic pulmonary fibrosis in Chile: a daily time series analysis. Chest 158 (2), 630–636.

Di, Q., Dai, L., Wang, Y., Zanobetti, A., Choirat, C., Schwartz, J.D., Dominici, F., 2017. Association of short-term exposure to air pollution with mortality in older adults. JAMA 318 (24), 2446–2456.

Faner, R., Rojas, M., Macnee, W., Agustí, A., 2012. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 186 (4), 306–313.

Faustini, A., Rapp, R., Forastiere, F., 2014. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. Eur. Respir. J. 44 (3), 744–753.

Goobie, G.C., Nouraie, M., Zhang, Y., Kass, D.J., Ryerson, C.J., Carlsten, C., Johannson, K.A., 2020. Air pollution and interstitial lung diseases: defining epigenomic effects. Am. J. Respir. Crit. Care Med. 202 (9), 1217–1224.

Goobie, G.C., Saha, P.K., Carlsten, C., Gibson, K.F., Johannson, K.A., Kass, D.J., Ryerson, C.J., Zhang, Y., Robinson, A.L., Presto, A.A., Nouraie, S.M., 2023. Ambient ultrafine particulate matter and clinical outcomes in fibrotic interstitial lung disease. Am. J. Respir. Crit. Care Med. 209 (9), 1082–1090.

Guan, W.J., Zheng, X.Y., Chung, K.F., Zhong, N.S., 2016. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. Lancet 388 (10054), 1939–1951.

Gümüşlü, S., Bilmen, S., Korgun, D.K., Yargiçoğlu, P., Ağar, A., 2001. Age-related changes in antioxidant enzyme activities and lipid peroxidation in lungs of control and sulfur dioxide exposed rats. Free Radic. Res. 34 (6), 621–627.

Hesterberg, T.W., Bunn, W.B., McClellan, R.O., Hamade, A.K., Long, C.M., Valberg, P.A., 2009. Critical review of the human data on short-term nitrogen dioxide ($NO_2$) exposures: evidence for $NO_2$ no-effect levels. Crit. Rev. Toxicol. 39 (9), 743–781.

Hilberg, O., Bendstrup, E., Løkke, A., Ibsen, R., Fløe, A., Hyldgaard, C., 2018. Co-morbidity and mortality among patients with interstitial lung diseases: a population-based study. Respirology 23 (6), 606–612.

Johannson, K.A., Balmes, J.R., Collard, H.R., 2015. Air pollution exposure: a novel environmental risk factor for interstitial lung disease? Chest 147 (4), 1161–1167.

Kreuter, M., Hoffmann-Vold, A.M., Bendstrup, E., 2021. Interstitial lung diseases: quo vadis? Lancet Respir. Med. 9 (10), 1084–1087.

Li, Z., Wang, J., Li, C., Gupta, P., Cribb, M., 2023. Ground-level gaseous pollutants ($NO_2$, $SO_2$, and CO) in China: daily seamless mapping and spatiotemporal variations. Atmos. Chem. Phys. 23, 1511–1532.

Liang, L., Cai, Y., Lyu, B., Zhang, D., Chu, S., Jing, H., Rahimi, K., Tong, Z., 2022. Air pollution and hospitalization of patients with idiopathic pulmonary fibrosis in Beijing: a time-series study. Respir. Res 23 (1), 81.

Liu, Y., Pan, J., Zhang, H., Shi, C., Li, G., Peng, Z., Ma, J., Zhou, Y., Zhang, L., 2019b. Short-term exposure to ambient air pollution and asthma mortality. Am. J. Respir. Crit. Care Med. 200 (1), 24–32.

Liu, J., Shi, C., Sun, S., Liang, J., Yang, Z.-L., 2019a. Improving land surface hydrological simulations in China using CLDAS meteorological forcing data. J. Meteor. Res-Prc 33 (6), 1194–1206.

Liu, T., Zhou, Y., Wei, J., Chen, Q., Xu, R., Pan, J., Lu, W., Wang, Y., Fan, Z., Li, Y., Xu, L., Cui, X., Shi, C., Zhang, L., Chen, X., Bao, W., Sun, H., Liu, Y., 2022. Association between short-term exposure to ambient air pollution and dementia mortality in Chinese adults. Sci. Total Environ. 849, 157860.

Mathai, S.C., Danoff, S.K., 2016. Management of interstitial lung disease associated with connective tissue disease. BMJ 352, h6819.

Meng, Z., Qin, G., Zhang, B., Geng, H., Bai, Q., Bai, W., Liu, C., 2003. Oxidative damage of sulfur dioxide inhalation on lungs and hearts of mice. Environ. Res. 93 (3), 285–292.

Motamedi, M., Ferrara, G., Yacyshyn, E., Osman, M., Abril, A., Rahman, S., Netchiporouk, E., Gniadecki, R., 2023. Skin disorders and interstitial lung disease: part I-screening, diagnosis, and therapeutic principles. J. Am. Acad. Dermatol. 88 (4), 751–764.

Orellano, P., Reynoso, J., Quaranta, N., 2021. Short-term exposure to sulphur dioxide ($SO_2$) and all-cause and respiratory mortality: a systematic review and meta-analysis. Environ. Int. 150, 106434.

Reno, A.L., Brooks, E.G., Ameredes, B.T., 2015. Mechanisms of heightened airway sensitivity and responses to inhaled $SO_2$ in asthmatics. Environ. Health Insights 9 (1), 13–25.

Rice, M.B., Li, W., Schwartz, J., Di, Q., Kloog, I., Koutrakis, P., Gold, D.R., Hallowell, R. W., Zhang, C., O'Connor, G., Washko, G.R., Hunninghake, G.M., Mittleman, M.A., 2019. Ambient air pollution exposure and risk and progression of interstitial lung abnormalities: the Framingham Heart Study. Thorax 74 (11), 1063–1069.

Sack, C., Vedal, S., Sheppard, L., Raghu, G., Barr, R.G., Podolanczuk, A., Doney, B., Hoffman, E.A., Gassett, A., Hinckley-Stukovsky, K., Williams, K., Kawut, S., Lederer, D.J., Kaufman, J.D., 2017. Air pollution and subclinical interstitial lung disease: the multi-ethnic study of atherosclerosis (MESA) air-lung study. Eur. Respir. J. 50 (6).

Sesé, L., Nunes, H., Cottin, V., Sanyal, S., Didier, M., Carton, Z., Israel-Biet, D., Crestani, B., Cadranel, J., Wallaert, B., Tazi, A., Maître, B., Prévot, G., Marchand-Adam, S., Guillot-Dudoret, S., Nardi, A., Dury, S., Giraud, V., Gondouin, A., Juvin, K., Borie, R., Wislez, M., Valeyre, D., Annesi-Maesano, I., 2018. Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. Thorax 73 (2), 145–150.

Tran, H.M., Tsai, F.J., Lee, Y.L., Chang, J.H., Chang, L.T., Chang, T.Y., Chung, K.F., Kuo, H.P., Lee, K.Y., Chuang, K.J., Chuang, H.C., 2023. The impact of air pollution on respiratory diseases in an era of climate change: a review of the current evidence. Sci. Total Environ. 898, 166340.

Turner, M.C., Andersen, Z.J., Neira, M., Krzyzanowski, M., Malmqvist, E., González Ortiz, A., Kiesewetter, G., Katsouyanni, K., Brunekreef, B., Melén, E., Ljungman, P., Tolotto, M., Forastiere, F., Dendale, P., Price, R., Bakke, O., Reichert, S., Hoek, G., Pershagen, G., Peters, A., Querol, X., Gerometta, A., Samoli, E., Markevych, I., Basthiste, R., Khreis, H., Pant, P., Nieuwenhuijsen, M., Sacks, J.D., Hansen, K., Lymes, T., Stauffer, A., Fuller, G.W., Boogaard, H., Hoffmann, B., 2023. Clean air in Europe for all! Taking stock of the proposed revision to the ambient air quality directives: a joint ERS, HEI and ISEE workshop report. Eur. Respir. J. 62 (4), 1700397.

Viegi, G., Taborda-Barata, L., 2022. A series of narrative reviews on air pollution and respiratory health for Pulmonology: why it is important and who should read it. Pulmonology 28 (4), 243–244.

Wang, X., Deng, X., Wu, Y., Qian, Z., Cai, M., Li, H., Lin, H., 2023. Low-level ambient sulfur dioxide exposure and genetic susceptibility associated with incidence of idiopathic pulmonary fibrosis: a national prospective cohort study. Chemosphere 337, 139362.

Wei, J., Li, Z., Li, K., Dickerson, R.R., Pinker, R.T., Wang, J., Liu, X., Sun, L., Xue, W., Cribb, M., 2022a. Full-coverage mapping and spatiotemporal variations of ground-level ozone ($O_3$) pollution from 2013 to 2020 across China. Remote Sens. Environ. 270, 112775.

Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., Su, T., Cribb, M., 2021a. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136.

Wei, J., Li, Z., Xue, W., Sun, L., Fan, T., Liu, L., Su, T., Cribb, M., 2021b. The ChinaHigh$PM_{10}$ dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. Environ. Int. 146, 106290.

Wei, J., Liu, S., Li, Z., Liu, C., Qin, K., Liu, X., Pinker, R.T., Dickerson, R.R., Lin, J., Boersma, K.F., Sun, L., Li, R., Xue, W., Cui, Y., Zhang, C., Wang, J., 2022b. Ground-level $NO_2$ surveillance from space across china for high resolution using interpretable spatiotemporally weighted artificial intelligence. Environ. Sci. Technol. 56 (14), 9988–9998.

Wells, A.U., Denton, C.P., 2014. Interstitial lung disease in connective tissue disease–mechanisms and management. Nat. Rev. Rheuma. 10 (12), 728–739.

Wijsenbeek, M., Suzuki, A., Maher, T.M., 2022. Interstitial lung diseases. Lancet 400 (10354), 769–786.

Xu, R., Huang, S., Shi, C., Wang, R., Liu, T., Li, Y., Zheng, Y., Lv, Z., Wei, J., Sun, H., Liu, Y., 2023. Extreme temperature events, fine particulate matter, and myocardial infarction mortality. Circulation 148 (4), 312–323.

Xu, R., Wang, Q., Wei, J., Lu, W., Wang, R., Liu, T., Wang, Y., Fan, Z., Li, Y., Xu, L., Shi, C., Li, G., Chen, G., Zhang, L., Zhou, Y., Liu, Y., Sun, H., 2022a. Association of short-term exposure to ambient air pollution with mortality from ischemic and hemorrhagic stroke. Eur. J. Neurol. 29 (7), 1994–2005.

Xu, R., Wei, J., Liu, T., Li, Y., Yang, C., Shi, C., Chen, G., Zhou, Y., Sun, H., Liu, Y., 2022b. Association of short-term exposure to ambient $PM_1$ with total and cause-specific cardiovascular disease mortality. Environ. Int. 169, 107519.

Yun, Y., Hou, L., Sang, N., 2011. $SO_2$ inhalation modulates the expression of pro-inflammatory and pro-apoptotic genes in rat heart and lung. J. Hazard Mater. 185 (1), 482–488.