Observational studies: Ambient air pollution and hospitalization for RA-ILD in a heavily polluted city in China

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Abstract

Little is known within the medical community about the impact of air pollution on hospital admissions due to rheumatoid arthritis associated with interstitial lung disease (RA-ILD). Our research aimed to explore whether there is a correlation and to estimate how the association was distributed across various lags in Jinan, China.

The relationships between ambient air pollutant concentrations, including PM2.5, PM10, sulfur dioxide (SO2), ozone (O3), and nitrogen dioxide (NO2), and monthly hospitalizations for RA-ILD were studied by employing a general linear model with a Poisson distribution. This time-series study was performed from January 1st, 2015 to December 31st, 2019.

In the 5-year study, there were 221 hospitalizations for RA-ILD in Jinan city. The levels of PM2.5, PM10, SO2, and NO2 were significantly related to the number of admissions for RA-ILD. PM2.5, PM10, and SO2 showed the most significant effect on the month (lag 0), and NO2 was most related to RA-ILD at a lag of two months (lag 2). The monthly admissions of RA-ILD increased by 0.875% (95% CI: 0.375–1.377%), 0.548% (95% CI: 0.148–0.949%), 1.968% (95% CI: 0.869–3.080%), and 1.534% (95% CI: 0.305–2.778%) for each 10 μg/m³ increase in PM2.5, PM10, SO2 and NO2, respectively.

This study might add more detailed evidence that higher levels of PM2.5, PM10, SO2 and NO2 increase the risk of hospitalizations for RA-ILD. Further study of the role of air pollution in the pathogenesis of RA-ILD is warranted.

Abbreviations:

anti-MAA = anti-malondialdehyde-acetaldehyde adduct, CI = Confidence interval, COPD = chronic obstructive pulmonary disease, EPA = the Environmental Protection Authority, ER = Excess risks, GAM = the generalized additive model, HIS = the Hospital Information System, HRCT = high-resolution CT, IL-1 = interleukin-1, IL-6 = interleukin-6, ILD = Interstitial lung disease, NF-κB = nuclear factor kappa-B, NO2 = Nitrogen dioxide, O3 = Ozone, RA = Rheumatoid Arthritis, RA-ILD = Rheumatoid arthritis associated with Interstitial lung Disease, SO2 = Sulfur dioxide, Th1 = T helper lymphocyte type 1, TNF-α = tumor necrosis factor alpha.

Keywords: air pollution, hospital admission, interstitial lung disease: rheumatoid arthritis, time-series analysis

1. Introduction

Rheumatoid arthritis (RA) is a disease related to chronic autoimmunity that has various systemic features and immune-mediated multiorgan dysfunction, characterized by symmetrical arthritis and synovitis. The common extra-articular organs involved include the cardiovascular system, lung, kidney, blood system, etc., in approximately 50% of patients with RA.[1,2]

Interstitial lung disease (ILD) is the main manifestation of lung
Involvement, and approximately 5–10% of all patients with RA will suffer clinically significant ILD. [13,4]

Compared with patients who have RA without ILD, patients with RA-ILD have a three-fold increase in mortality. This means that RA-ILD has a poor prognosis, as reported. [11] ILD dramatically influence patients’ lives with an average survival of just 3 years from diagnosis of RA-ILD, which accounting for 10%-20% of all deaths associated with RA. [15,5,6] The underlying etiologies of RA-ILD are unknown. Early studies have reported that risk factors leading to RA-ILD consist of increased age, male sex, smoking, higher RA disease activity, and seropositivity for RA autoantibodies. [13,4,7,8,9] Additionally, current research has shown that atmospheric pollutants are risk factors for both RA and ILD of known or unknown etiology, although the mechanism is unclear. [10,11] However, little correlational research has been performed between atmospheric pollutants and ILD in RA.

Air pollution is a risk for the occurrence of negative respiratory results. Air pollutants of particulate matter (PM2.5, a pollutant with a diameter not more than 2.5 μm), PM10 (a pollutant with a diameter not more than 10 μm), and NO2, SO2, and O3 which can deposit deeply in the airways and alveoli causing oxidative stress, inflammation and tissue injury. [12,13] Research has shown that environmental exposure factors may activate innate immune cells, alter the pulmonary microenvironment and activate a cascade of pro-inflammatory and immunity-related responses that eventually cause ILD or other models of lung involvement in patients with RA. [14-16] This suggests that environmental factors are crucial during the occurrence of RA-ILD. We hypothesized that exposure to air pollution would be associated with RA-ILD.

Jinan is the economic and population center of Shandong Province, which is considered one of the regions in China with the most severe air pollution problem. There is no previous survey regarding the relationships between major air pollutants and RA-ILD in China, and we conducted time-series research to analyze the associations between air pollutants and hospitalization for RA-ILD for the first time in Jinan, China.

2. Materials and methods

2.1. Study area

Jinan is the political center of Shandong Province and among China’s most polluted cities. Jinan has a distinctive topography surrounded by mountains, and the surrounding terrain is higher than the urban area, which shows a basin state. Such a topographic feature is more likely to form a “temperature inversion” phenomenon, contributing to the pollutants not being discharged and spreading outward, which can easily lead to the accumulation of air pollutants.

As the economy has soared and leveled off, the population has significantly grown and traffic has become more congested, Jinan has been plagued by serious problems of air pollution in recent years. The discharge of automobile exhaust, pollutants from heavy industrial enterprises and living sources and the combustion of coal in urban areas are all the primary sources of air pollutants, and they are excessively concentrated in urban areas with poor diffusion conditions. These situations have caused a considerable burden on pollution control and environmental protection in Jinan. In addition, the residents of Jinan require heating in winter, and coal-fired heating increases pollution emissions. At the same time, low temperatures and low wind levels are not conducive to the diffusion and dilution of pollutants. All these reasons have led to severe, frequent haze incidents in Jinan in recent years. The research area is the entire Jinan region in my research.

2.2. Air pollution data

Monthly average data on the concentration of ambient air pollutants were acquired from 14 fixed air quality monitoring stations situated in Jinan, Shandong Province, China, during the duration of the research period from January 1st, 2015, to December 31st, 2019. The data provide the daily and monthly maximum, minimum, and mean concentrations for PM2.5, PM10, SO2, NO2, and O3. Those 14 ambient air quality monitoring stations are distributed all over Jinan and obtain air pollution measurements every day. After the calculation of the daily average of each contamination from the 14 stations, the monthly mean levels of these contaminations are analyzed. All the data collected were calculated and analyzed by the Environmental Protection Authority (EPA) in Jinan city.

2.3. Hospital admission data

Records of hospital admission were collected from the computerized database from the Hospital Information System (HIS) of The First Affiliated Hospital of Shandong’s First Medical University in Shandong Province. The coverage of this hospital is the entire Jinan. The records collected include information on sex, age, admission date, diagnosis, the address, and the address of residence. All the patients admitted due to RA-ILD during our research period in Jinan city. All the data were sufficiently reliable and accurate for use in our research. We limited our study to patients who had resided in Jinan for a long time to ensure the accuracy of the regional study, and we excluded patients who were rehospitalized within one month to limit exposure misclassifications. In addition, all subjects consented to study participation after receiving notification and study information, and all aspects of study data were approved by the ethics committee of Shandong First Medical University.

3. Methods

In this research, the correlation between the mean concentrations of ambient air pollutants and hospitalizations due to RA-ILD was analyzed by employing the generalized additive model (GAM) with the Poisson distribution as the link function, which has reliable and satisfactory performance in previous studies. [18,19] In this research, the generalized additive model of the time series can be used to explore the “lag effect” and “cumulative lag effect” on the basis of evaluating the correlation between various atmospheric pollutants and the number of patients admitted to the hospital.
Each pollutant concentration is put into the basic model as a continuous variable, and a single-pollutant model is established. The generalized additive model with Poisson distribution as the link function was employed to analyze the relationship between the concentration of various air pollutants and the number of hospitalizations for RA-ILD, the weight of which equals the hospital admission counts on that day. After adjusting for the confounders, including the long-term trend, temperature, and relative humidity, the association between them was estimated using the excess risk (ER) and 95% confidence interval (CI).

Positive ER values indicated the percentage increase (%) in RA-ILD monthly admissions for an increase in pollutant concentration. Negative ER values indicate that there is a negative effect or no correlation between air pollutants and hospital admissions. All statistical analyses were conducted with R package software.

In addition, the number of inpatients with the disease may change immediately after the change in exposure factors, or there may be a gradual change in response after a certain period of exposure, that is, a lag effect. Considering the existence of a lag effect, we recorded the month of air pollutant measurement as lag time zero (lag 0), a lag of one month as lag 1, and so on. We also conducted sensitivity analyses to demonstrate the effect of air pollutants on the disease under different cumulative lag days to verify the stability of the results. A cumulative lag of one month is lag01, and a cumulative lag of two months is lag02. The derived GAM equation is as follows:

$$\log[\text{Estimated number of RA-ILD admissions}] = \alpha + \beta_1C_i + s(\text{Time}, df) + s(\text{RH}, df) + s(\text{Temp}, df)$$  \hspace{1cm} (1)

where $Y_t$ shows the number of patients admitted on day $t$, and $E(Y_t)$ indicates the estimated number of patients on that day. $\beta_1$ represents the regression coefficient, $s$ represents the spline smoothing function, and $C_i$ represents the average pollutant concentration of the day or lag (i) month. $\text{Time}$ represents the long-term trend, $\text{RH}$ represents monthly average relative humidity, and $\text{Temp}$ represents monthly average temperature.

The value for the degrees of freedom ($df$) of the long-term trend is based on the Akaike information criterion (AIC). In this model, the value for the degrees of freedom corresponding to the minimum value of the AIC is the best $df$ value. We choose 7 per year as the value for the degrees of freedom of the smoothing function of data variables.

4. Result

During this 5-year study, there were 221 hospitalizations for RA-ILD in Jinan city. Table 1 presents the descriptive statistics data for monthly hospital admissions due to RA-ILD in different sexes, age ranges, and monthly environmental statistics. The monthly average concentrations for PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, and O$_3$ were 66.9 $\mu $g/m$^3$, 127.8 $\mu $g/m$^3$, 28.2 $\mu $g/m$^3$, 46.9 $\mu $g/m$^3$, and 107.2 $\mu $g/m$^3$, respectively.

Spearman’s correlation coefficients related to the air pollutants are shown in Table 2. The correlation between individual pollutants is reflected in Table 2. The results showed a positive correlation among PM$_{2.5}$, PM$_{10}$, SO$_2$, and NO$_2$. In contrast, there was an apparent negative correlation between the other pollutants and O$_3$, and the results were statistically significant. ($p < 0.01$). Especially high correlations were found between PM$_{2.5}$ and PM$_{10}$ ($R = 0.884$), PM$_{2.5}$ and SO$_2$ ($R = 0.881$), PM$_{10}$ and SO$_2$ ($r = 0.824$), and O$_3$ and NO$_2$ ($R = 0.843$).

Table 3 reveals the estimated effects of air pollutants on hospitalizations for RA-ILD in single-pollutant models. The results showed that the levels of PM$_{2.5}$, PM$_{10}$, SO$_2$ and NO$_2$ were significantly associated with the number of admissions for RA-ILD. A tendency for higher O$_3$ levels to be inversely associated with hospitalizations for RA-ILD was observed. PM$_{2.5}$, PM$_{10}$, and SO$_2$ showed the strongest effect on the month (lag 0), and NO$_2$ was most related to RA-ILD at a lag of two months (lag 2). The monthly admissions of RA-ILD increased by 0.875% (95% CI: 0.375–1.377%), 0.548% (95% CI: 0.148–0.949%), 1.968% (95% CI: 0.869–3.080%), and 1.534%...

### Table 1

| Variable | Mean ± SD | Min | Max | P25 | P50 | P75 |
|----------|-----------|-----|-----|-----|-----|-----|
| Total ($N=221$) | 3.68 ± 1.75 | 1.00 | 8.00 | 3.00 | 3.00 | 5.00 |
| Sex | | | | | | |
| Male ($n=92$) | 1.53 ± 1.21 | 0.00 | 5.00 | 1.00 | 1.00 | 2.00 |
| Female ($n=129$) | 2.13 ± 0.17 | 1.00 | 5.00 | 1.25 | 2.00 | 3.00 |
| Age | | | | | | |
| <65 ($n=140$) | 2.33 ± 0.98 | 0.00 | 5.00 | 2.00 | 2.00 | 3.00 |
| ≥65 ($n=81$) | 1.35 ± 0.97 | 0.00 | 4.00 | 1.00 | 1.00 | 2.00 |
| Air pollutant concentrations (monthly average) | | | | | | |
| PM$_{2.5}$ ($\mu $g/m$^3$) | 66.90 ± 28.10 | 26.00 | 158.00 | 42.25 | 61.00 | 81.75 |
| PM$_{10}$ ($\mu $g/m$^3$) | 127.87 ± 40.71 | 53.00 | 232.00 | 98.00 | 124.00 | 152.50 |
| SO$_2$ ($\mu $g/m$^3$) | 28.15 ± 19.08 | 8.00 | 92.00 | 13.25 | 22.50 | 34.75 |
| NO$_2$ ($\mu $g/m$^3$) | 46.85 ± 11.85 | 26.00 | 73.00 | 35.50 | 46.50 | 55.75 |
| O$_3$ ($\mu $g/m$^3$) | 107.23 ± 47.84 | 27.00 | 206.00 | 64.00 | 108.00 | 144.75 |
| Weather conditions (monthly average) | | | | | | |
| Temperature(°C) | 15.43 ± 9.84 | -1.50 | 29.10 | 5.05 | 16.15 | 25.27 |
| Humidity (%) | 55.12 ± 11.52 | 35.70 | 82.00 | 46.30 | 54.70 | 62.78 |

Max = maximum value, Min = minimum value, P25 = 25th percentile, P50 = 50th percentile, P75 = 75th percentile, SD = standard deviation. $n$ = number of observations. * monthly average.
study also showed that O3 was associated with an increased risk of RA and interstitial lung disease. Lucile Sesé et al. found that cumulative exposure to PM10 and PM2.5 increased the mortality of patients with IPF. Coralynn Sack et al. found that for every 40 ppb increase in NO2, the probability of developing ILD increased 1.77 times (95% CI from 1.06 to 2.95). Higher concentrations of pollutant exposure were associated with faster disease progression. Christopher J et al. found that there was a close relationship between the level of PM10 and the decline in FVC in patients with ILD; for every 1 μg increase in PM10 in exposed patients, FVC decreased an additional 46 ml/year.

All the research above indicates a correlation between air pollutants and RA or ILD, and although it cannot prove an association between air pollutants and RA-ILD, we can hypothesize that air pollutants may also result in an increase in the incidence of RA-ILD through unknown mechanisms. However, in our research, it was found that there was an adverse association between O3 exposure and the incident risks of RA-ILD. The correlation analysis between ambient air pollution showed a positive correlation between PM2.5, PM10, SO2, and NO2 and an apparent negative correlation with O3, and the results were statistically significant. The chemical coupling bond between O3 and NO2 in the atmosphere may explain the situation mentioned above. The degrees of exposure to O3 and NO2 are inextricably linked. O3 can be scavenged by traffic-produced NO2, and O3 is a harmful secondary pollutant produced by the reaction of volatile compounds in the troposphere with sunlight, which will lead to the consumption of NO2 and the accumulation of O3. Higher exposure to NO2 always occurred with lower O3 exposure. That is, individuals who were often exposed to high levels of NO2 were also exposed to low levels of O3. This negative association could be the reason for the trend towards an adverse correlation between higher levels of O3 and lower incident risks of RA-ILD. In other words, O3 is not a protective factor for RA-ILD.

The risk factors for RA-ILD reported in previous studies include older age, male sex, smoking, exposure to occupational dust and the existence of multiple RA-related autoantibodies, including RF, ACPA, anti-heat-shock protein-90 (anti-HSP90) antibodies, anti-PAD antibodies and anti-malondialdehyde-acetaldehyde adduct (anti-MAA) antibodies. Existing studies have found that smoking can promote the citrullination of proteins in the lungs, which can cause damage to the lungs and drive the

### Table 2

| Variable | PM2.5 | PM10 | SO2 | NO2 | O3 |
|----------|-------|------|-----|-----|----|
| PM2.5    | 1.000 | 0.884* | 0.881* | 0.748* | −0.731* |
| PM10     | −     | 1.000 | 0.824* | 0.733* | −0.689* |
| SO2      | −     | −     | 1.000 | 0.581* | −0.556* |
| NO2      | −     | −     | −     | 1.000 | −0.843* |
| O3       | −     | −     | −     | −     | 1.000 |

*Statistically significant.

(95% CI: 0.305–2.778%) for each 10 μg/m³ increase in PM2.5, PM10, SO2 and NO2, respectively.

Table 4 shows that when exposed to high concentrations of PM2.5, PM10, NO2 and SO2, the cumulative 0- to 2-month admissions for RA-ILD had the strongest effect.

### 5. Discussion

This forward-looking epidemiological time-series study in Jinan, China, with documented exposure to air pollution, showed the correlation between air pollutants and hospitalization related to RA-ILD. We found that exposure to PM2.5, PM10, SO2, and NO2 aggravated the excess risk of hospitalization for RA-ILD. However, higher O3 tended to be inversely associated with hospitalization for RA-ILD. There is good reason to believe that lowering ambient air pollution concentration would lead to improvements in the health of people with RA-ILD.

No previous studies investigating the correlation between air pollutants and hospitalization for RA-ILD exist. Thus, we have performed an original study in this field, particularly for prolonged lag. Previous studies have mainly analyzed the correlation between air pollutants and RA or ILD of known or unknown etiology, although such studies are very limited, and the outcomes have not always been consistent.

Hart JE et al. found a 30% elevated risk of RA in participants whose homes were located near the road, who are more likely to be living within an environment with pollutants associated with traffic, revealing a possible etiological role of air pollution. Similar studies have been conducted in Canada. Studies have shown that exposure to traffic-related pollutants such as PM2.5, NO, and NO2 increases the risk of rheumatoid arthritis. The study also showed that O3 was associated with an increased risk of rheumatoid joints. Another case-control study showed a correlation between NO2 and SO2 exposure and the growing risk of RA, but there was no evidence of a growing risk of RA because of PM10. In a recent 12-year case-control study in Korea involving 2220 subjects, O3 and CO exposure was positively correlated with the risk of RA in adults over 20 years of age. A retrospective cohort study from Taiwan Province showed that participants exposed to higher annual average pollutant concentrations of NO2 and PM2.5 had a growing risk of RA, and environmental factors may be a risk factor for rheumatoid arthritis. However, the other 2 studies had contrary observations.

The influence of air pollution is certain under numerous respiratory conditions, including poorly controlled asthma, increased incidence of chronic obstructive pulmonary disease (COPD), and respiratory-related mortality. At present, there are also many studies showing the correlation between air pollutants and interstitial lung disease. Lucile Sesé et al. found that cumulative exposure to PM10 and PM2.5 increased the mortality of patients with IPF. Coralynn Sack et al. found that for every 40 ppb increase in NO2, the probability of developing ILD increased 1.77 times (95% CI from 1.06 to 2.95). Higher concentrations of pollutant exposure were associated with faster disease progression. Christopher J et al. found that there was a close relationship between the level of PM10 and the decline in FVC in patients with ILD; for every 1 μg increase in PM10 in exposed patients, FVC decreased an additional 46 ml/year.

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### Table 3

| Variable | Lag0       | Lag1       | Lag2       |
|----------|------------|------------|------------|
| PM2.5    | 0.875 (0.375,1.377) | 0.355 (−0.120,0.832) | 0.705 (0.188,1.224) |
| PM10     | 0.548 (0.148,0.949) | 0.132 (−0.217,0.482) | 0.401 (0.044,0.759) |
| SO2      | 1.968 (0.869,3.080) | 0.478 (−0.212,1.174) | 0.885 (0.148,1.634) |
| NO2      | 1.461 (0.262,2.675) | 1.478 (0.272,2.699) | 1.534 (3.052,7.778) |
| O3       | −0.304 (−0.019,0.589) | −0.379 (−0.085,0.671) | −0.393 (−0.093,0.694) |
The development of RA.\[1\] However, studies have also shown an increase in the citrullination of lung proteins in people who are not smokers.\[2\] This finding indicates that other substances can enter the lung from the outside through breathing, such as silicon dioxide, air pollutants and various microorganisms. They may have a mutual impact on genes and the immune mechanism to stimulate the production of ACPA or to promote the relevant immune response in patients with RA.\[1\][4,41] This evidence is enough to show that environmental factors are crucial in the occurrence of RA-ILD.

The pathophysiology of RA-related lung diseases is complex and rare. According to the existing research, the concept of “gene-environment interactions with immune system interactions” is followed.\[42\] Notably, some studies have shown that the lungs play a role in the mechanism of air pollutants affecting the pathogenesis of RA. Airway and alveolar epithelial cells are the first line of defense against inhaled substances, such as smoking-associated toxicants, air pollutants and pathogens, which are potential primary triggers of mucosal injury through the local lung and systemic oxidative stress and inflammation.\[43,44\] Air pollutants inhaled in the respiratory tract, such as PM or gaseous pollutants, can stimulate neutrophils and mononuclear macrophages to release free reactive oxygen species, thereby activating nuclear factor kappa-B (NF-kB).\[45,46\] NF-kB is a key regulator of pro-inflammatory cytokines in patients with rheumatoid arthritis. NF-kB can stimulate multiple cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), to produce excess T helper lymphocyte type 1 (Th1) cells and induce a pulmonary inflammatory response.\[46\] There is persistent, amplified, chronic inflammation, which, in susceptible individuals with positive HLA-DRB1 shared epitopes, interacts with environmental factors. Protein citrullination occurs in the lungs, which further produces ACPA and then achieves a personal evaluation of exposure to air pollution and hospitalization due to RA-ILD.

In summary, we found that an increased number of hospitalizations for RA-ILD was associated with long-term exposure to air pollutants, including PM\textsubscript{2.5}, PM\textsubscript{10}, SO\textsubscript{2}, NO\textsubscript{2} and NO\textsubscript{2}. These findings provide supporting evidence that ambient air pollutants might be a potential risk factor for RA-ILD. Despite the positive results presented here, we could not entirely give evidence of a clear mechanism to explain pollutant effects on RA-ILD. Further studies are needed to investigate the potential biological pathways underlying these associations to help identify potential contributing factors to the morbidity or progression of RA-ILD.

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Author contributions
YFH, BJL and LY contributed to the study conception, analysis plan, supervised data analysis and revised the drafted paper. BJL and SGZ cleaned and analysed the data, drafted and revised the paper; All authors approved the submitted version of this paper.

References
[1] Zhang Yangwen. Detection of serum RF and anti-CCP antibody concentrations in rheumatoid arthritis and their significance. Journal of Practical Medicine 2015;31:108–9.
[2] Turesson C, O’Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extra-articular disease manifestations is associated with
excess mortality in a community-based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62–7.

[3] Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Rhu JHC. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583–91.

[4] Koduri G, Norton S, Young A, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology 2010;49:1483–9.

[5] Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350–7.

[6] Silvonen S, Korpela M, Laippala P, Mustonen J, Pasternak A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. Scand J Rheumatol 2004;33:221–7.

[7] Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics - a large multicentre UK study. Rheumatology 2014;53:1676–82.

[8] Sparks JA, He X, Huang J, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. Arthritis Rheumatol 2019;71:1472–82.

[9] Kiely P, Busby AD, Nikiphorou E, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERA5 and ERAN inception cohorts. BMJ Open 2018;8:e020866.

[10] Essouma M, Noubiap JJ. Is air pollution a risk factor for rheumatoid arthritis? J Inflamm 2015;12:48.

[11] Sack C, Vedal S, Sheppard L, et al. Air pollution and subclinical interstitial lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA) air-lung study. Eur Respir J 2017;50:1700983.

[12] Hirawat K, van Eeden SF. Contribution of lung macrophages to the inflammatory responses induced by exposure to air pollutants. Mediators Inflamm 2013;2013:619523.

[13] Johansson KA, Vittinghoff E, Lee K, et al. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. Eur Respir J 2014;43:1124–31.

[14] Catrina AI, Ytterby A, Reynisdottir G, Malmstrom V, Klæreskog L. Lungs, joints and immunity against citrullinated proteins in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:645–53.

[15] Larsen JM, Steen-Jensen DB, Laursen JM, et al. Divergent pro-inflammatory profile of human dendritic cells in response to commensal and pathogenic bacteria associated with the airway microbiota. PLoS One 2012;7:e31976.

[16] Thannickal VJ, Lavens GB, White ES, Lynch JP, Martinz FJ. Mechanisms of pulmonary fibrosis. Am Rev Respir Med 2004;55:395–417.

[17] Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

[18] Wiwatanadate P, Liwsrisakun C. Acute effects of air pollution on peak expiratory flow rates and symptoms among asthmatic patients in Chiang Mai, Thailand. Int J Hyg Environ Health 2011;214:251–7.

[19] Pothirat C, Tosukhowong A, Chaiwong W, Liwsrisakun C, Inchai J. Effects of seasonal smog on asthma and COPD exacerbations requiring emergency visits in Chiang Mai, Thailand. Asian Pac J Allergy Immunol 2016;34:284–9.

[20] Hart JE, Laden F, Puett RC, Costenbader KH, Karlson EW. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environmental Health Perspectives 2009;117:1065–9.

[21] De Roos AJ, Koehoorn M, Tamburic L, Davies HW, Brauer M. Proximity to traffic, ambient air pollution, and community noise in relation to incident rheumatoid arthritis. Environ Health Perspect 2014;122:1075–80.

[22] Hart JE, Kallberg H, Laden F, et al. Ambient air pollution exposures and risk of rheumatoid arthritis: results from the Swedish EIRA case-control study. Ann Rheum Dis 2013;72:888–94.

[23] Shin J, et al. Association between Exposure to Ambient Air Pollution and Rheumatoid Arthritis in Adults.”. International Journal of Environmental Research and Public Health 2019;16:1227.

[24] Chang K, Hsu C, Muo C, et al. Air pollution exposure increases the risk of rheumatoid arthritis: a longitudinal and nationwide study. Environ Int 2016;94:495–501.

[25] Hart JE, Kallberg H, Laden F, et al. Ambient air pollution exposures and risk of rheumatoid arthritis. Arthritis Care Res 2013;65:1190–6.

[26] Gan RW, Deane KD, Zerbe GO, et al. Relationship between air pollution and positivity of RA-related autoantibodies in individuals without established RA: a report on SERA. Ann Rheum Dis 2013;72:888–94.

[27] Mann J, Balmes JR, Bruckner TA, et al. Short-term effects of air pollution on wheeze in asthmatic children in Fresno. California Environ Health Perspect 2010;118:1497–502.

[28] Schikowski T, Sugiri D, Ranft U, et al. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respir Res 2005;6:152.

[29] Dominici F, Peng RD, Bell MI, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 2006;295:1127–34.

[30] Jerrett M, Burnett RT, Pope CA, et al. Long-term ozone exposure and mortality. N Engl J Med 2009;360:1085–95.

[31] Søse L, Nunes H, Cottin V, et al. Israel-Biet D et al. Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. Thorax 2018;73:145–50.

[32] Winterbottom CJ, Shah RJ, Patterson KC, et al. Exposure to ambient particulate matter is associated with accelerated functional decline in idiopathic pulmonary fibrosis. Chest 2018;153:1221–8.

[33] Brunekeef B, Holgate ST. Air pollution and health. Lancet 2002;360:1233–42.

[34] Clapp LJ, Jenkins ME. Analysis of the Relationship between Ambient Levels of O3, NO2, and NO as a Function of NOx in the UK. Atmos Environ 35: 6391–6405.

[35] Brito Y, Glassberg MK, Aschnerman DP. Rheumatoid arthritis-associated interstitial lung disease: current concepts. Curr Rheumatol Rep 2017;19:79.

[36] Harlou L, Gochuico BR, Rosas JO, et al. Anti-citrullinated heat shock protein 90 antibodies identified in bronchoalveolar lavage fluid are a marker of lung-specific immune responses. Clin Immunol 2014;156:60–70.

[37] Giles JT, Darrah E, Danoff S, et al. Association of cross-reactive antibodies targeting peptidyl-arginine deiminase 3 and 4 with rheumatoid arthritis-associated interstitial lung disease. PLoS ONE 2014;9:e97894.

[38] England BR, Duryee MJ, Roul P, et al. Malondialdehyde-acetaldehyde adducts and antibody responses in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2019;71:1483–93.

[39] Damgaard D, Friberg Bruun Nielsen M, Quisgaard Gaunsbaek M, Palarasah Y, Svane-Knudsen V, Nielsen CH. Smoking is associated with increased levels of extracellular peptidylarginine deiminase 2 (PAD2) in the lungs. Clin Exp Rheumatol 2015;33:405–8.

[40] Reynisdottir G, Karim K, Joshua V, et al. Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive Rheumatoid Arthritis. Arthritis Rheumatol 2014;66:31–9.

[41] Sparks JA, Karlson EW. The roles of cigarette smoking and the lung in the transitions between phases of preclinical Rheumatoid Arthritis. Curr Rheumatol Rep 2016;18:15.

[42] Klæreskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid Arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by catrullination. Arthritis Rheum 2006;54:38–46.

[43] Ruiz-Esquide V, Sannarti R. Tobacco and other environmental risk factors in rheumatoid arthritis. Reumatol Clin 2012;8:342–50.

[44] Ritz SA. Air pollution as a potential contributor to the ‘epidemic’ of autoimmune disease. Med Hypotheses 2010;74:110–7.

[45] Farhat SCL, Silva CA, Orione MAM, Campos LMA, Sallum AME, Braga ALF. Air pollution in autoimmune rheumatic diseases: a review. Autoimmunity Rev 2011;11:14–21.

[46] Ying G, Wang Y, Cen XM, Yang M, Liang Y, Xie QB. Lipid peroxidation-mediated inflammation promotes cell apoptosis through activation of NF-κB pathway in rheumatoid arthritis synovial cells. Mediators Inflamm 2015;2015:640310.

[47] Restrepo JF, del Roncon I, Battafarano DF, Haas RW, Doria M, Escalante A. Clinical and laboratory factors associated with interstitial lung disease in Rheumatoid Arthritis. Clin Rheumatol 2015;34:1529–36.

[48] Willis VC, Demoruelle MK, Derber LA, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. Arthritis Rheum 2013;65:2545–54.