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Research article

# Ambient fine particulate matter is associated with daily outpatient visits for ankylosing spondylitis: A time-series analysis in Beijing, China

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A B S T R A C T

Exposure to ambient fine particulate matter ($PM_{2.5}$) has a great impact on human body's immune system, but the correlation between $PM_{2.5}$ and ankylosing spondylitis has not yet been clarified. We extracted 58,600 outpatient visits for ankylosing spondylitis from the Beijing Medical Claim Data for Employees database from 2010 to 2017. The percentage of outpatient visits following $PM_{2.5}$ concentrations was estimated using generalized additive models with Poisson connections. Increase by 10 μ g/m$^3$, $PM_{2.5}$ is associated with daily outpatient visits for ankylosing spondylitis. In this test, the average concentration of $PM_{2.5}$ was 86.8 ± 74.3 μ g/m$^3$. For every 10 μg/m$^3$ increase in $PM_{2.5}$ concentration, there was a 0.34% (95% CI, 0.26–0.42%) increase in the risk of patients who visited the doctor on the same day. Females and younger patients were most susceptible to the impact of $PM_{2.5}$ exposure ($P < 0.05$). This study revealed the relationship between exposure to $PM_{2.5}$ and ankylosing spondylitis, and future research can further confirm this finding and explore the potential mechanisms.

## 1. Introduction

The pathogenesis of ankylosing spondylitis (AS) is still unclear, and the disease is mainly characterized by involvement of the spine and sacroiliac joints, causing bone remodeling disorders and muscle rigidity [1]. In addition, AS also has significant external joint symptoms, such as uveitis, psoriasis and intestinal diseases [2]. The onset of ankylosing spondylitis is insidious, and the clinical diagnosis is difficult. At present, there is no specific diagnosis and treatment method, and the treatment is mainly to relieve the symptoms of patients and delay the progress of the disease. Moreover, AS tends to occur in young adults, and in severe cases, people lose their ability to work, which has caused the consumption of substantial medical resources and has brought serious economic burden and psychological pressure to patients and families. The pathogenesis of AS is not completely clear and may be caused by the

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combination of autoinflammation and autoimmune factors [1]. It has been established that environmental factors, especially air pollution, can increase the risk of or result in a poor response to medications for autoinflammatory and immune diseases, such as rheumatoid arthritis [3,4], psoriasis [5], and chronic inflammatory joint disease [6]. The reason for this association may be that air pollutants, which can cause oxidative stress through the lungs, induce a large number of antibodies and autoreactive T lymphocytes or induce epigenetic changes that eventually lead to the development of autoimmune diseases [7]. However, the relationship between air pollution and AS is uncertain.

Air pollution is an important contributor to the major disease burden globally, especially in low- and middle-income countries [8]. Fine particulate matter ($PM_{2.5}$), which refers to particulate matter with an aerodynamic diameter of ≤2.5 μm, is considered the most detrimental air pollutant to human health among all the types of air pollution [9]. China has been facing air pollution for a long time [10]. According to the National Environmental Protection Agency (EPA), in 2016, over 81% of China's population was exposed to air pollution levels exceeding 35 μg/$m^3$, the recommended environmental standard [11]. In 2017, the number of deaths due to $PM_{2.5}$ pollution in China was 851,660 (712,002–990,271) [12].

Only two other studies have been undertaken to examine the relationship between $PM_{2.5}$ and AS. In the first study, Iranian scholars enrolled 30 AS patients and confirmed that long-term exposure to $PM_{2.5}$ (mean concentrations of $PM_{2.5}$ during the study period were 26.4–30 μg/$m^3$) was associated with worse disease outcomes [13]. However, in another study, a Korean study involving 88 patients with AS found no significant association between $PM_{2.5}$ exposure (the maximum concentration of $PM_{2.5}$ during the study period was 31.7 μg/$m^3$) and AS [14]. Both studies had small sample sizes and low mean $PM_{2.5}$ concentrations, which may have contributed to underrepresentation. Therefore, the relationship between AS and $PM_{2.5}$ is still not clear. Outpatient consultation is the most common method of consultation for AS patients, and it is an important indicator reflecting the short-term relationship between air pollution and the disease. The aim of this study was to explore the short-term exposure to $PM_{2.5}$ and AS patients by a time series approach. This paper is a pioneering, large-scale population-based survey of $PM_{2.5}$ concentrations and AS in China.

## 2. Methods

### 2.1. Data for AS patients

We obtained daily outpatient data for ankylosing spondylitis (AS) from Beijing's Medical Claims for Employees database (BMCDE) during the period of January 1, 2010 to December 31, 2017. This database records the medical expenses of all beneficiaries of the Beijing Urban Residents Basic Medical Insurance Scheme. Due to the small rural population and high employment in Beijing, urban residents' medical insurance is the largest form of medical insurance in Beijing. The database comprises demographic features such as age and gender, medical information such as hospital level and name, dates of visits, Chinese disease diagnosis and corresponding ICD-10 codes (M45) based on the International Classification of Diseases, dates of diagnoses, and cost information. For more comprehensive information on the database, please refer to the relevant literature [15,16].

Because BMCDE only collects reimbursement data and removes all personal identifiers, we only used encrypted tracking information. Therefore, the study did not require ethical review.

### 2.2. Environmental data

The China Meteorological Administration provided meteorological data for this survey, including daily temperature and relative humidity. The $PM_{2.5}$ concentration of this survey was announced by the US embassy. Studies have found that the $PM_{2.5}$ levels monitored by the US embassy are about the same as the local conditions, and the validity and reliability of the data have been demonstrated in detail in previous work [17–19]. The radiation radius refers to the effective range monitored by $PM_{2.5}$ monitoring station, which covers most of the tertiary hospitals in Beijing, accounting for 97.8% (44/45), 79.3% (69/87) in most secondary hospitals [20]. In addition, some previous studies have also confirmed that the data monitored by the US embassy is credible [19,21]. China included $PM_{2.5}$ in the national ambient air quality monitoring system in 2013, and released real-time monitoring data. Therefore, the data provided by the US embassy is the only source of daily $PM_{2.5}$ data. Specifically, the study used daily $PM_{2.5}$ concentrations (24 h) to express exposure to the population.

### 2.3. Statistical analysis

We used a time-series design to analyse $PM_{2.5}$ concentrations and adult outpatient visits for AS (adjusted for meteorological variables).

In line with prior research on the correlation between air pollution and health, we utilized a generalized additive Poisson model that incorporates the following equation [20,22,23]:

$$\boldsymbol{Log[E(Y_t)] = \alpha + \beta PM_{2.5t} + public\ holiday_t + day\ of\ the\ week_t + ps(calendar\ time_t, 7\ per\ year) + ps(temperature_t, 6) + ps(relative\ humidity_t, 3)}$$

where $E(Y_t)$ is the expected number of outpatient visits of the AS patient on day t; ps is utilized as a penalty spline function, while categorical variables such as public holidays and days of the week are adjusted in the analysis. This is consistent with previous studies examining the relationship between air pollution and health.; β represents the incidence of AS and the concentration unit of $PM_{2.5}$ is related to the increase (relative risk); and α is the intercept. To verify the robustness of the results, we not only selected the degrees of freedom of calendar time, relative humidity, and temperature according to previous studies but also conducted sensitivity analyses on the results for different degrees of freedom [22]. In addition, we also included stratified analyses (by gender, age, and season) of the lagged effect of each 10 μg/$m^3$ increase in $PM_{2.5}$ concentration on the increase in outpatient visits for AS.

To investigate the exposure-response relationship between $PM_{2.5}$ and adult ankylosing spondylitis (AS) outpatients clinic, we constructed independent models ranging from the day of the clinic (lag 0) to three days before (lag 3), as well as multiple-day delays (lag 0–1 to lag 0–3) [24]. We also performed stratified analyses to detect potential changes in the impact of different age groups (patients aged 18–64 years old and above≥65 years old), gender (male and female), and seasons (cool season and warm season) on AS risk [25].

The data analysis was conducted utilizing the 'mgcv' and 'nlme' packages in R3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). To establish the linkage between daily outpatient visits for ankylosing spondylitis (AS) and a 10 μg/$m^3$ increase in $PM_{2.5}$ concentration, we utilized percentage change and 95% confidence intervals (CIs). We regarded a two-sided difference of $p \leq 0.05$ as statistically significant. Categorical variables are expressed as percentages, while continuous variables are expressed as the mean ± standard deviation.

## 3. Results

Basic demographic characteristics of the ankylosing spondylitis (AS) patients included in this study are presented in Table 1. From January 1, 2010, to December 31, 2017, there were 58,600 outpatient visits to AS clinics in Beijing, of which 50.03% were recorded from April to September. Most patients were male (40,997, 69.96%). There were 54,205 cases of patients under 65 years old, and 4395 cases of patients over 65 years old, which were 92.50% and 7.50% respectively.

Table 2 provides a summary of the daily $PM_{2.5}$ concentrations, and weather data throughout the study period. The table indicates that the average daily $PM_{2.5}$ concentration was 99.5 ± 75.3) μg/$m^3$, and the average temperature was 12.6 °C ± 11.6 °C. Additionally, the relative humidity was 48.6% ± 20.3%.

The changes in the number of outpatient visits to AS are shown in Table 3 for every 10 units increase in $PM_{2.5}$ concentration with different lag times. After controlling for the four variables of temperature, relative humidity, day of the week, and public holidays, for every 10 μg/$m^3$ increase in $PM_{2.5}$ concentration on that day, the number of AS outpatient visits increased by 0.34% (95% CI, 0.26–0.42%). Our findings revealed a distinct exposure-response relationship between ankylosing spondylitis (AS) and $PM_{2.5}$ concentrations for lags of 1, 2, and 3 days, with corresponding variations of 0.22% (95% CI, 0.16–0.29%), 0.13% (95% CI, 0.07–0.19%), and 0.16% (95% CI, 0.10–0.22%). It was found that there was a strong association between the concentration of $PM_{2.5}$ and the number of outpatient visits for AS, and the maximum lag time was 0–3 days (0.41%; 95% CI, 0.31–0.50%). At the time of the analysis, we found that the effect size was larger from 1 to 3 days than other days, and the effect size gradually decreased after 3 days, so we did not show it.

Table 4 presents the outcomes of the stratified analyses, corresponding to men and patients aged over 65 years, the estimated effect of $PM_{2.5}$ was larger in women (0.65%, 95% CI: 0.51–0.79%) and patients aged 18–64 years (0.36%, 95% CI: 0.27–0.44%). Additionally, the estimated value for the warm season was higher (0.47%, 95% CI: 0.33–0.62%) than that for the cool season (0.21%, 95% CI: 0.11–0.30%).

Table 5 exhibits the outcomes of the sensitivity analysis. Altering the degrees of freedom for calendar time, temperature, and relative humidity did not lead to any significant modifications in the percentage estimates. Therefore, there is a certain association between $PM_{2.5}$ and outpatient treatment of AS.

## 4. Discussion

Overall, our study aimed to explore the association between $PM_{2.5}$ concentrations and ankylosing spondylitis (AS) outpatient visits in Beijing, China. Through the adjustment of several potential confounding factors (such as temperature, relative humidity, day of the week, calendar time, and public holidays), we found that a 10 μg/$m^3$ increase in $PM_{2.5}$ concentration was linked to a 0.34% (95% CI, 0.26–0.42%) increase in outpatient visits on the same day. Moreover, females and patients under 65 years old were more susceptible to an increase in $PM_{2.5}$ levels. This is the first large-scale population-based survey in China that explores the correlation between $PM_{2.5}$ concentrations and the acute effects of outpatient visits associated with ankylosing spondylitis. Our results can provide valuable experience for other countries or cities that also experience severe air pollution and provide a new intervention target for the

**Table 1**
Characteristics of outpatient visits for ankylosing spondylitis between January 1, 2010 and December 31, 2017 in Beijing, China.

| Variable | All year | Cool season | Warm season |
|---|---|---|---|
| Outpatient visits | 58600 | 29282 ± 49.97 | 29318 ± 50.03 |
| Sex | | | |
| Male(%) | 40997(69.96) | 20500(70.01) | 20493(69.90) |
| Female(%) | 17603(30.04) | 8782(29.99) | 8825(30.10) |
| Age(year) | | | |
| 18–64(%) | 54205(92.50) | 27103(92.56) | 27102(92.44) |
| ≥65(%) | 4395(7.50) | 2179(7.44) | 2216(7.56) |

**Table 2**
Distribution of daily fine particulate matter ($PM_{2.5}$) concentrations, and meteorological conditions.

| Variable | Mean ± SD | Minimum | Percentile | | | Maximum | IQR |
|---|---|---|---|---|---|---|---|
| | | | 25th | 50th | 75th | | |
| $PM_{2.5}$(μg/m$^3$) | 86.8 ± 74.3 | 1.0 | 33.3 | 66.5 | 115.0 | 537.3 | 81.7 |
| Temperature(°C) | 14.6 ± 11.3 | −14.3 | 2.6 | 15.1 | 24.0 | 34.5 | 21.4 |
| Relative humidity (%) | 51.8 ± 20.2 | 8.0 | 35.1 | 52.0 | 68.1 | 88.0 | 33.0 |

IQR: interquartile range. SD: standard deviation.

**Table 3**
Increases in outpatient visits for ankylosing spondylitis associated with a 10-μg/m$^3$ increase in levels of fine particulate matter ($PM_{2.5}$) for different lag structures.

| Lag day | Percentage change | 95% confidence interval | *P* |
|---|---|---|---|
| Lag 0 day | 0.34 | 0.26–0.42 | <0.001 |
| Lag 1 day | 0.22 | 0.16–0.29 | 0.001 |
| Lag 2 day | 0.13 | 0.07–0.19 | 0.029 |
| Lag 3 day | 0.16 | 0.10–0.22 | 0.009 |
| Lag 4 day | 0.30 | −0.10–0.70 | 0.4547 |
| Lag 5 day | 0.08 | −0.33–0.48 | 0.8503 |
| Lag 0–1 days | 0.40 | 0.31–0.49 | <0.001 |
| Lag 0–2 days | 0.38 | 0.29–0.47 | <0.001 |
| Lag 0–3 days | 0.41 | 0.31–0.50 | <0.001 |
| Lag 0–4 days | 0.40 | −0.22–1.02 | 0.5228 |
| Lag 0–5 days | 0.41 | −0.25–1.07 | 0.5345 |

**Table 4**
Increases in outpatient visits for ankylosing spondylitis associated with a 10-μg/m$^3$ increase in lag 0–3 fine particulate matter ($PM_{2.5}$) and stratified by sex, age group, and season.

| Subgroups | Percentage change | 95% confidence interval | *P* |
|---|---|---|---|
| Gender | | | 2.17*10-7 |
| Male | 0.21 | 0.12–0.30 | |
| Female | 0.65 | 0.51–0.79 | |
| Age(year) | | | 0.0093 |
| 18-64 | 0.36 | 0.27–0.44 | |
| ≥65 | −0.01 | −0.27–0.26 | |
| Season | | | 0.0033 |
| Cool | 0.21 | 0.11–0.30 | |
| Warm | 0.47 | 0.33–0.62 | |

*P* value was obtained by Z-test for the difference between the two risk estimates derived from subgroup analyses.

**Table 5**
Percentage changes with 95% confidence intervals in outpatient visits for ankylosing spondylitis associated with a 10 μg/m$^3$ increase in fine particulate matter ($PM_{2.5}$) concentration on the same day by different degrees of freedom (df) for calendar time, temperature, and relative humidity.

| Variable | *df* | Percentage change | 95% confidence interval | *P value* |
|---|---|---|---|---|
| Calendar time | 6 | 0.34 | 0.26–0.42 | <0.001 |
| | 7[a] | 0.27 | 0.19–0.35 | 0.001 |
| | 8 | 0.26 | 0.18–0.34 | 0.001 |
| | 9 | 0.29 | 0.21–0.38 | <0.001 |
| Temperature | 5 | 0.34 | 0.26–0.42 | <0.001 |
| | 6[a] | 0.34 | 0.26–0.42 | <0.001 |
| | 7 | 0.34 | 0.26–0.42 | <0.001 |
| | 8 | 0.34 | 0.26–0.42 | <0.001 |
| Relative humidity | 3[a] | 0.34 | 0.26–0.42 | <0.001 |
| | 4 | 0.34 | 0.26–0.42 | <0.001 |
| | 5 | 0.34 | 0.26–0.42 | <0.001 |
| | 6 | 0.34 | 0.26–0.42 | <0.001 |

[a] The *df* value used in this study model.

prevention and control of AS.

Until now, there have been only two studies on the link between the risk and severity of $PM_{2.5}$ and AS. However, the two conclusions are not exactly the same. A case-control study conducted by Iranian scholars showed that long-term exposure to $PM_{2.5}$ significantly worsens joint pain and stiffness in patients with ankylosing spondylitis, and significantly reduces physical function [13]. However, a survey of South Korean cities showed AS had no significant link to continued exposure to $PM_{2.5}$ [14]. We believe that the relatively low $PM_{2.5}$ concentration (median $PM_{2.5}$ concentration: 31.7 μg/$m^3$) in this study may account for the inconsistency with our findings. In addition, the study investigated the impact of environmental fine particulate matter on a range of autoimmune rheumatic diseases, including rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythematosus. In the study, the incidence of each disease was mutually exclusive because follow-up stopped when participants first developed one of the diseases. This may also underestimate the independent effect of $PM_{2.5}$ on ankylosing spondylitis. In addition, the composition of $PM_{2.5}$ can differ by geographical location due to various factors such as industrial activities, traffic emissions, meteorological conditions, and natural sources. For example, urban areas with heavy traffic tend to have higher levels of $PM_{2.5}$ derived from vehicle exhaust emissions, whereas regions near industrial sites may be more influenced by industrial emissions. The composition of $PM_{2.5}$ plays a crucial role in determining the health effects associated with exposure. Certain components, such as heavy metals, organic compounds, and polycyclic aromatic hydrocarbons (PAHs), are more harmful to human health than others. For instance, long-term exposure to $PM_{2.5}$ containing high levels of PAHs has been linked to an increased risk of respiratory diseases, cardiovascular problems, and even cancer [26–28]. The difference in $PM_{2.5}$ composition is also one of the reasons for the inconsistent results between the two studies.

Ghazouani concluded, based on an analysis of relevant data of major greenhouse gas-emitting countries in Europe, that improving relevant laws and regulations can effectively reduce the overall level of pollution [29]. Similarly, since 2013, the Chinese government has successfully issued relevant policies to control $PM_{2.5,}$ for example, (1) making further improvements to regulate and control $PM_{2.5}$; (2) establishing a system to monitor $PM_{2.5}$ and other air pollutants; (3) strengthening efforts to control pollution from motor vehicle exhaust; and (4) strictly controlling the emission of volatile organic compounds from commercial enterprises [30]. China's air pollution situation has greatly improved in recent years under these comprehensive measures. According to statistics compiled by the Beijing Municipal Ecology and Environment Bureau, in April 2021, the average concentration of $PM_{2.5}$ in the air of Beijing was 31 μg/$m^3$, a year-by-year decrease of approximately 69% compared with the average concentration of $PM_{2.5}$ (99.5 ± 75.3 μg/$m^3$) in Beijing during the study period (2010–2012) [31]. At the same time, this further highlights the strength of our study. Because our study included data from periods of high pollution, which enables an evaluation of the

Exposure-response association between a wide range of $PM_{2.5}$ concentrations and outpatients visits for ankylosing spondylitis comprehensively. We look forwards to more research in the future to compare the changes related to AS and $PM_{2.5}$ before and after the improvements in air quality.

Gender, age, and season were taken into account for variables affecting the number of visits to ankylosing spondylitis after $PM_{2.5}$ exposure. Our study revealed that the detrimental effects of $PM_{2.5}$ were more notable in patients aged 18–64 years compared to older patients aged 65 and over ($P = 0.012$). Similar findings have been reported in a study of rheumatoid arthritis [3]. However, the only two studies we were able to find on the association between AS and air pollution did not stratified the analysis by age, so the results should be taken with caution and validated in future studies [13,14]. In the present study, we observed higher estimates of the impact of $PM_{2.5}$ on female patients. Studies have shown that women are more sensitive to symptoms of illness and are more likely to seek medical attention [32,33]. Furthermore, we observed a stronger association between $PM_{2.5}$ concentration and outpatient visits for ankylosing spondylitis (AS) during the summer season compared to the winter season. Based on our findings, we recommend that women and young people between the ages of 18–64 use personal protection when going outside during periods of high pollution. In the warm season, people should also be cautious about exposure to air pollutants.

There are few literature reports on how $PM_{2.5}$ affects the occurrence and development of ankylosing spondylitis. Air pollutants may affect autoimmune processes in multiple ways. Studies have confirmed that inhalation of air pollutants can cause oxidative stress and induce broncho-related lymphoid tissue to affect T and B cells, leading to the production of pro-inflammatory cytokines. In addition, air pollutants can induce epigenetic changes, which can lead to the development of autoimmune diseases [34,35]. To put it differently, the inhalation of particulate matter can lead to mitochondrial degeneration and permanent alterations in the epigenome [36]. Moreover, air pollutants trigger the maturation of antigen-presenting cells by stimulating the release of soluble inflammatory mediators, and continuous inhalation of pollutants exacerbates this process [37]. From another point of view, one of the main reasons for the increase in outpatient visits after short-term $PM_{2.5}$ exposure could be the increase in ankylosing spondylitis-associated pain that results from serious air pollution [38].

The study has some limitations. One limitation of our study is that we lacked access to data on other air pollutants such as nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), carbon monoxide (CO), ozone ($O_3$), and particulate matter with an aerodynamic diameter ≤10 μm ($PM_{10}$), which prevented us from analyzing the independent effect of $PM_{2.5}$. It has been suggested that future research should study the association between AS and other pollutants. Second, people obtain the amount of human exposure through air pollution monitoring stations in fixed outdoor places, which will cause errors in the measurement results and underestimate the impact of air pollution. Others argue that future research should more precisely measure people's exposure to air pollution, perhaps by collecting data on those who wear air-pollution monitors. Another potential limitation of our study is that the Beijing Medical Claim Data for Employees database solely includes data from patients aged 18 years or older. Therefore, our findings may underestimate the adverse effects of air pollution on the younger population. It has been recommended that children and adolescents under the age of 18 should be included in future studies to make the estimate of the impact of $PM_{2.5}$ on health more accurate. Lastly, considering that AS often occurs in early adulthood (17–45 years old), future studies should focus on analyzing the association between the incidence of AS and $PM_{2.5}$ levels in patients aged 17–45 years. In the future, we can further expand the sample size and conduct national-level surveys. Overall, our findings should be interpreted carefully, and future studies should investigate the independent impact of $PM_{2.5}$ pollution.

## 5. Conclusions

The results of this study found a significant correlation between short-term exposure to $PM_{2.5}$ and the number of outpatient visits for ankylosing spondylitis. Future research can further explore the independent effects and interactions of other types of pollutants, and further supplement new evidence on the impact of the atmospheric environment on human health.

## Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because the data used in the study were collected for administrative purpose without any personal identifiers.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because the dataset belongs to the government, but they are available from the corresponding author upon a reasonable request.

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## CRediT authorship contribution statement

**Hongbo Chen:** Conceptualization. **Junhui Wu:** Data curation. **Ruotong Yang:** Formal analysis. **Huan Yu:** Formal analysis. **Shaomei Shang:** Conceptualization. **Yonghua Hu:** Conceptualization.

## Declaration of competing interest

There is no conflict of interest.

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