ORIGINAL RESEARCH

Explore the Relationship Between Short-Term Ambient Air Pollution Exposure and Daily Outpatient Visits for Metabolic Related Fatty Liver

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Background: Many studies have shown that the pollution of fine particles in the air is related to the incidence of chronic diseases. However, research on air pollution and metabolism-associated fatty liver disease (MAFLD) is limited.

Objective: The purpose of this study was to explore the relationship between short-term ambient air pollution and daily outpatient visits for metabolic-related fatty liver.

Methods: We used a quasi-Poisson regression generalized additive model to stratify analyses by season, age, and gender.

Results: From January 1, 2017, to August 31, 2019, 10,562 confirmed MAFLD outpatient visits were recorded. A 10 μg/m^3 increase of fine particular matter (PM10and PM2.5) and NO_2 concentrations corresponding with percent change were 0.82 (95% confidence interval [CI], 0.49–1.15), 0.57 (95% CI, 0.18–0.98), and 0.86 (95% CI, 0.59–1.13) elevation in MAFLD outpatient visits. In terms of season, the impact estimates of NO_2 and PM2.5% change were 3.55 (95% CI, 1.23–5.87) and 1.12 (95% CI, 0.78–1.46) in the hot season and transition season, respectively. Compared with the warm season, the impact estimates of PM10were more significant in the cool season: 2.88 (95% CI, 0.66–5.10). NO_2 has the greatest effect in the transition season, whereas PM10 has the greatest highest effect in the cool and hot seasons. Compared with other pollutants, PM2.5 has the greatest impact in the age stratification, which percent change are 2.69 (95% CI, 0.77–5.61) and 2.88 (95% CI, 0.37–6.40) respectively. The impact values of PM2.5 in male and female percent change were 3.60 (95% CI, 0.63–6.57) and 1.65 (95% CI, 1.05–2.25), respectively.

Conclusion: This study shows that the air pollutants are related to the number of outpatient visits for MAFLD. The effects of different air pollutants on MAFLD outpatient visits were different by season, ages, and gender.

Keywords: air pollutants, metabolism-associated fatty liver disease, generalized additive model

Introduction

Metabolism-associated fatty liver disease (MAFLD) (formerly known as nonalcoholic fatty liver disease) is the leading cause of liver disease worldwide. Its diagnosis is based on the detection of hepatic steatosis (liver histology, noninvasive biomarkers, or imaging) and the presence of at least one of the three criteria, including clinical evidence of overweight or obesity, type 2 diabetes mellitus, or metabolic dysfunction, such as waist circumference and dyslipidemia or hyperglycemia Studies have shown that the prevalence of MAFLD has increased to a worrying level, creating a huge burden for individuals and the health care system.[1,2] In the past 20 years, MAFLD has developed from a relatively unknown disease to the most common chronic liver disease in the world. With rapid changes in lifestyle, the prevalence of MAFLD is considered to be increasing worldwide.[3,4] In a model study of eight countries, it was estimated that China's MAFLD population will increase by 29.1% between 2016 and 2030, reaching 3145.8 million cases.[5,6]

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The World Health Organization analyzed the burden of disease caused by air pollution, finding that more than two million premature deaths each year can be attributed to urban outdoor and indoor air pollution. Four common air pollutants include particulate matter (PM), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2).[7] The global burden of disease study identified air pollution as the main cause of global burden of disease, especially in developing countries.[8,9] Studies have shown that air pollution not only affects respiratory diseases, but also affects acute myocardial infarction, arrhythmia, conjunctivitis, and maletal disorders.[10,11]

In addition, studies have shown that long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 is positively associated with the prevalence of the metabolic syndrome.[12–14] More and more evidence shows that environmental pollutants such as diesel exhaust particulates, suspended PM, metals, and polychlorinated compounds are important risk factors for the development of MAFLD.[15] According to work by Tarantino et al, exposure to ambient air particles with an aerodynamic diameter of 2.5 mm or less (PM2.5) can enhance MAFLD. Therefore, the effect of environmental factors on liver disease has attracted much attention.[16] Up to now, some studies on the relationship between fatty liver disease and air pollution have been conducted in animals.[17–19] In this study, we performed a quasi-Poisson regression generalized additive model to analyze the relationship between short-term air pollution exposure and fatty liver disease based on outpatient visits to the Affiliated Hospital of Hangzhou Normal University in Hangzhou.

Materials and Methods
Air Pollution and Meteorological Data
Air quality monitoring stations are located in Hangzhou, providing daily values of PM2.5 (μg/m3), PM10 (μg/m3), SO_2 (μg/m3), O_3 (μg/m3), NO_2 (μg/m3), CO (μg/m3), relative humidity (%), and mean temperature (°C). The details of Affiliated Hospital of Hangzhou Normal University and specific air quality monitoring stations are shown in the Figure S1. The daily air pollution parameters and temperatures of Hangzhou between January 1, 2017, and August 31, 2019, were downloaded from the China Meteorological Administration website (http://data.cma.cn/). The daily concentrations are represented 24-hour averages, and the O3 concentration was the maximal 8-hour average from all valid monitoring sites in this study.

Study Population
Data for patients with MAFLD from January 2017 to August 2019 were collected from the outpatient database of Affiliated Hospital of Hangzhou Normal University. Patients diagnosed with MAFLD who attended outpatient visits were included in this study. A MAFLD diagnosis is based on the detection of hepatic steatosis (liver histology, noninvasive biomarkers, or imaging) and the presence of at least one of the three criteria, including clinical evidence of overweight or obesity, type 2 diabetes mellitus, or metabolic dysfunction, such as waist circumference and dyslipidemia or hyperglycemia.[20] According to the latest diagnostic standard conditions, the diagnostic program is written with R (The R Foundation R Foundation for Statistical Computing, Vienna, Austria) to re-diagnose the outpatient information recorded in the hospital outpatient database.

In this study, a total of 11,731 outpatient visits, 378 cases of missing information and error were excluded, and 791 cases not living in Hangzhou for a long time were also excluded. Finally, 10,562 outpatient visits with MAFLD were analyzed. The ethics committee of Affiliated Hospital of Hangzhou Normal University approved all the procedures performed in this study, and complied with the Declaration of Helsinki.

Statistical Methods
A generalized additive model (GAM) was used in the statistical analysis to analyze the data. Because daily hospital cases typically followed an over dispersed Poisson distribution, quasi-Poisson regression was used in the GAM.[21] Several covariates including natural splines were introduced to control their potential confounding effects. First, a natural cubic regression smoothing function of calendar time with 7 degrees of freedom (df) per year excluded unmeasured long-term and seasonal trends longer than two months. Second, a natural smooth function of the mean temperature (6 df) and relative humidity (3 df) controlled the nonlinear confounding effects of weather conditions. Third, indicator variables were implemented for "day of the week" and public holidays.[22] Briefly, the following log-linear GAM was fitted to obtain the estimated pollution log-relative rate β in the selected city:

$$logE(Y_t) = \beta Z_t + DOW + ns(time, df) + ns(temperature, 6) + ns(humidity, 3) + intercept$$

where $E(Y_t)$ is the expected number of MAFLD outpatient visits at day t; β is the log-related rate of MAFLD associated with a unit increase of air pollutants; Z_t is the pollutant concentrations at day t; DOW is a dummy variable for the day of the week; ns is the natural cubic regression smooth function.

All these cases were stratified by age (<45 and ≥45 years), by Gender (male female) and cool season (November to March), hot season (June to August), and transition season (April, May, September, and October).After establishing the basic model, single-pollutant models were initially used and introduced, a priori, in turn each air pollutant concentration on the concurrent day (lag0). Given that the health effects of ambient air pollutants could last for multiple days, more single lag days were used (lag0, lag1, lag2, lag3, lag4, lag5, and lag6), and the moving average exposure of multiple days (lag01, lag02, lag03, lag04, lag05, lag06, and lag07) were obtained. To verify the stability of the model, two-pollutant models were built to evaluate the stability of effect estimates after adjusting for the co-pollutants. Co-pollutants with a correlation coefficient < 0.7 were added to the two-pollutant model.

The effects are expressed as the percentage of change and 95% CI in daily hospital MAFLD outpatient visits per 10 μg/m3 increase in pollutant concentrations. The statistical tests were two-sided, and the effects with p < 0.05 were considered to be statistically significant. All statistical models were constructed using R software version 3.6.0 (R Foundation for Statistical Computing, version 3.6.1; http://www.Rproject.org) using the MGCV package.

Results

The basic descriptive statistics of the number of outpatient visits, pollutants, and meteorological data are shown in Table 1. From January 1, 2017, to August 31, 2019, 10,562 confirmed outpatient visits were reported. During this period, the average number of cases per day was 8.94, and the number of cases in winter was more than that in summer or transition seasons. During the study period, the daily average concentrations of NO_2, SO2, PM10, O_3, and PM2.5 were 48.43 μg/m3, 35.89 μg/m3, 56.80 μg/m3, 137.50 μg/m3, and 48.91 μg/m3, respectively. The daily average humidity and temperature were 75.21% and 18.45 °C, respectively.

Figure 1 shows significant differences among the five different air pollution indicators and number of outpatient visits in three different seasons. The daily air pollution concentration and the number of MAFLD outpatient visits (except O_3) are the greatest in the cool season and the lowest in the hot season. The number of outpatient visits is the greatest in hot seasons. The Spearman correlation coefficients of PM2.5, PM10, SO_2, and NO_2 were 0.68 to 0.95. The maximum 8-hour

Table 1 Summary Statistics of Daily Air Pollutants, Weather Conditions, and Number of Outpatient Visits Caused by MAFLD (N = 10,562) in Hangzhou from 2017.1 to 2019.08

	Mean
Air pollutant concentration (μg/m³)	
NO_2	48.43
O_3	137.5
PM10	56.80
PM2.5	48.91
SO_2	35.89
Meteorological measures	
Temperature (°C)	18.45
Humidity (%)	75.21
Age (Number of people)	
<45	9.14
≥45	8.74
Season (Number of people)	
Hot (Jun to Aug)	7.97
Transition (Apr, May, Sep and Oct)	8.50
Cool (Nov to Mar)	10.35
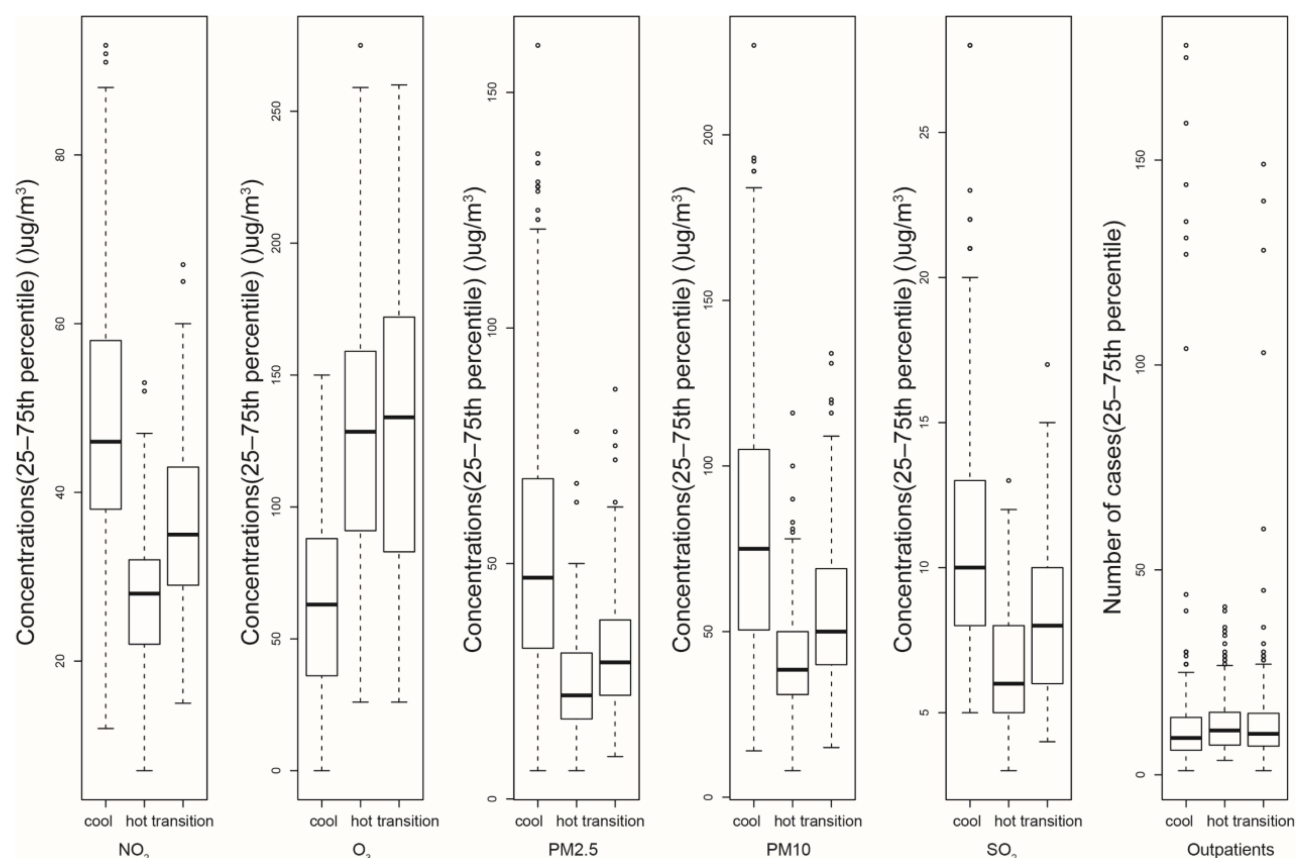
Figure 1 Box plots of five air pollutants in the cool, transition, warm seasons and outpatient visits cases. Boxes indicate the interquartile range (25–75th percentile); lines within boxes !indicate medians; whiskers below the boxes represent minimum values; whiskers and dots above the boxes indicate the maximum values.

mean O_3 concentration negatively correlated with PM2.5, PM10, SO_2, and NO_2 (Spearman correlation coefficient ranged from 0.27 to 0.06) (Figure 2).

In terms of seasons, the effect of ambient air pollution on the total number of outpatient visits with MAFLD shows significant differences among the three seasons (Table 2). The impact estimates of NO_2 and PM2.5 were 3.55 (95% CI, 1.23–5.87) and 1.12 (95% CI, 0.78–1.46) in the transition season, respectively. Compared with the warm season, the impact estimates of PM10 were more significant in the cool season: 2.88 (95% CI, 0.66–5.10). NO_2 has the greatest effect in the transition season, whereas PM10 has the greatest effect in the cool and hot seasons. Regarding age, the study shows an increase in the correlation percentage between NO_2, PM10, PM2.5, and the total number of outpatient visits with MAFLD varies with age groups. The older the age, the greater the impact estimate. In the two age groups with 45 years as the dividing line, PM2.5 has the highest impact estimate: 2.69 (95% CI, 0.77–5.61) and 2.88 (95% CI, 0.37–6.40), respectively. Regarding gender, compared with females, NO_2, PM10, and PM2.5 had a greater impact on males, especially PM2.5. The impact values of PM2.5 in male and female were 3.60 (95% CI, 0.63–6.57) and 1.65 (95% CI, 1.05–2.25), respectively.

Figure 3 shows the results obtained from the single-lag day (lag0–lag6) and cumulative exposure models (lag01–lag07) for the percent increase in MAFLD outpatient visits per 10 μg/m3 increase in pollutants. Statistically significant results were observed at lag 0–4 and 01–07 day for NO_2, lag 0 and 01–04 day for PM10, lag 0 and 01–03 day for PM2.5, and lag 01–03 day for SO_2. Table 3 shows the results of two-pollutant models using exposure at lag 01. The magnitudes of all five pollutants were stable The effect estimates of NO_2, PM10, and PM2.5 pollutants remained statistically significant when adjusting for co-pollutants.

Discussion

This study shows that the air pollutants in Hangzhou are related to the number of outpatient visits for MAFLD. The effects of different air pollutants on MAFLD outpatient visits were different for different seasons, ages, and genders. The most
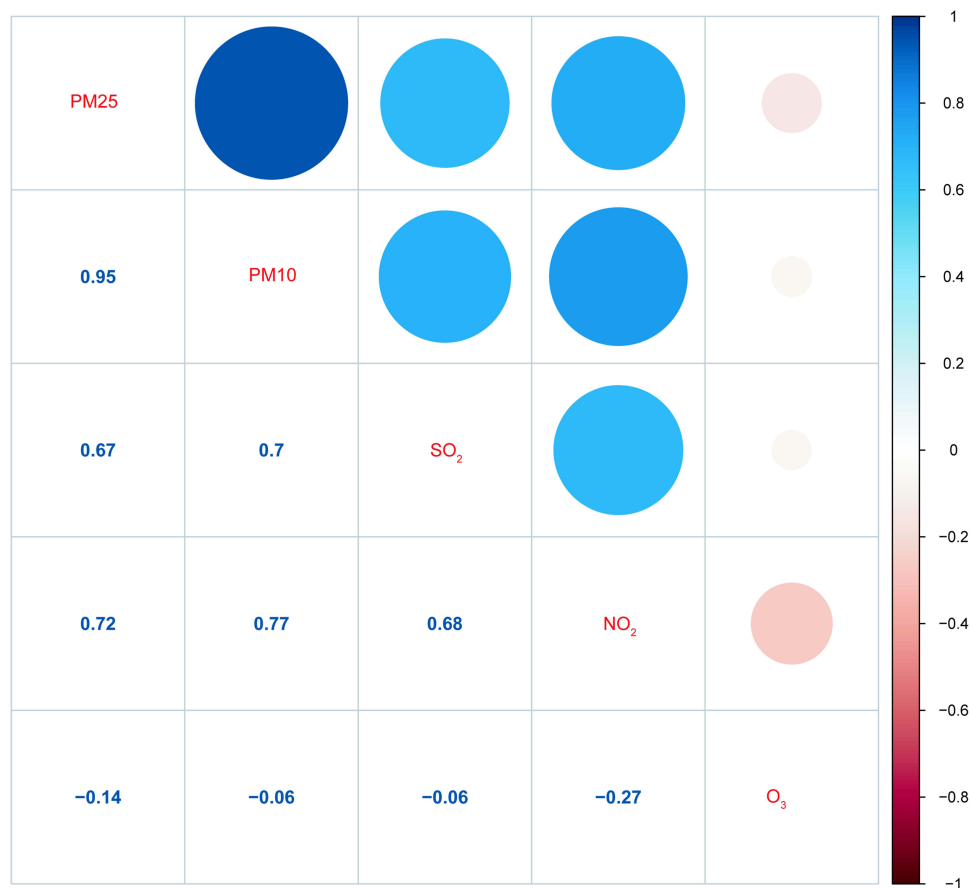
Figure 2 NO$_2$, O$_3$, PM10, PM2.5, and SO$_2$ correlation coefficient matrix.(The upper right corner matrix represents the correlation size, the lower left corner matrix is the correlation coefficient, and the right bar is the correlation coefficient contrast color).

significant associations of air pollution appeared on single days and the associations in the cumulative exposure models were still positive. Regarding seasonal variations, NO$_2$ showed the greatest effect in the transition season, whereas PM10 had the greatest effect in the cool and hot seasons. The effect of PM10 was more significant in the cool season. Regarding variations

Table 2 Percent Change (95% CI) in MAFLD Outpatient Visits Caused by Total, Season, Gender, and Age per 10 μg/m^3 Increase in Concentrations of Five Air Pollutants in Hangzhou, China

	Total	Season		
		Cool	**Hot**	**Transition**
NO$_2$	**0.86(0.59,1.13)**	**0.41(0.11,0.72)**	1.12(−0.76,3.01)	**3.55(1.23,5.87)**
O$_3$	−2.2(−3.00,-1.49)	−0.63(−3.90,2.64)	−0.53(−1.64,0.59)	−2.53(−4.69,-0.37)
PM10	**0.82(0.49,1.15)**	**2.88(0.66,5.10)**	**0.27(0.14,0.40)**	0.38(−1.30,206)
PM2.5	**0.57(0.18,0.98)**	2.92(−0.07,5.91)	−0.69(−5.02,2.44)	**1.12(0.78,1.46)**
SO$_2$	1.28(−0.05,2.80)	1.76(−1.42,4.94)	−1.26(−3.13,0.61)	0.23(−0.45,0.92)

	Age		Gender	
	<45	**≥45**	**Male**	**Male**
NO$_2$	**1.49(0.97,2.02)**	**2.47(0.86,4.09)**	**1.64(1.17,2.11)**	**1.14(0.53,1.75)**
O$_3$	−2.98(−4.51,-0.45)	−2.21(−4.06,-0.36)	−2.69(−4.26,1.12)	−1.75(−3.64,0.14)
PM10	**2.23(0.29,4.18)**	**2.44(2.09,4.79)**	**2.02(0.04,4.01)**	**0.66(0.22,3.10)**
PM2.5	**2.69(0.77,5.61)**	**2.88(0.37,6.40)**	**3.60(0.63,6.57)**	**1.65(1.05,2.25)**
SO$_2$	4.15(−7.49,15.79)	5.90(−1.60,13.40)	2.31(−3.75,8.37)	4.53(−2.59,11.65)

Note: Significant statistical estimates are highlighted in bold.
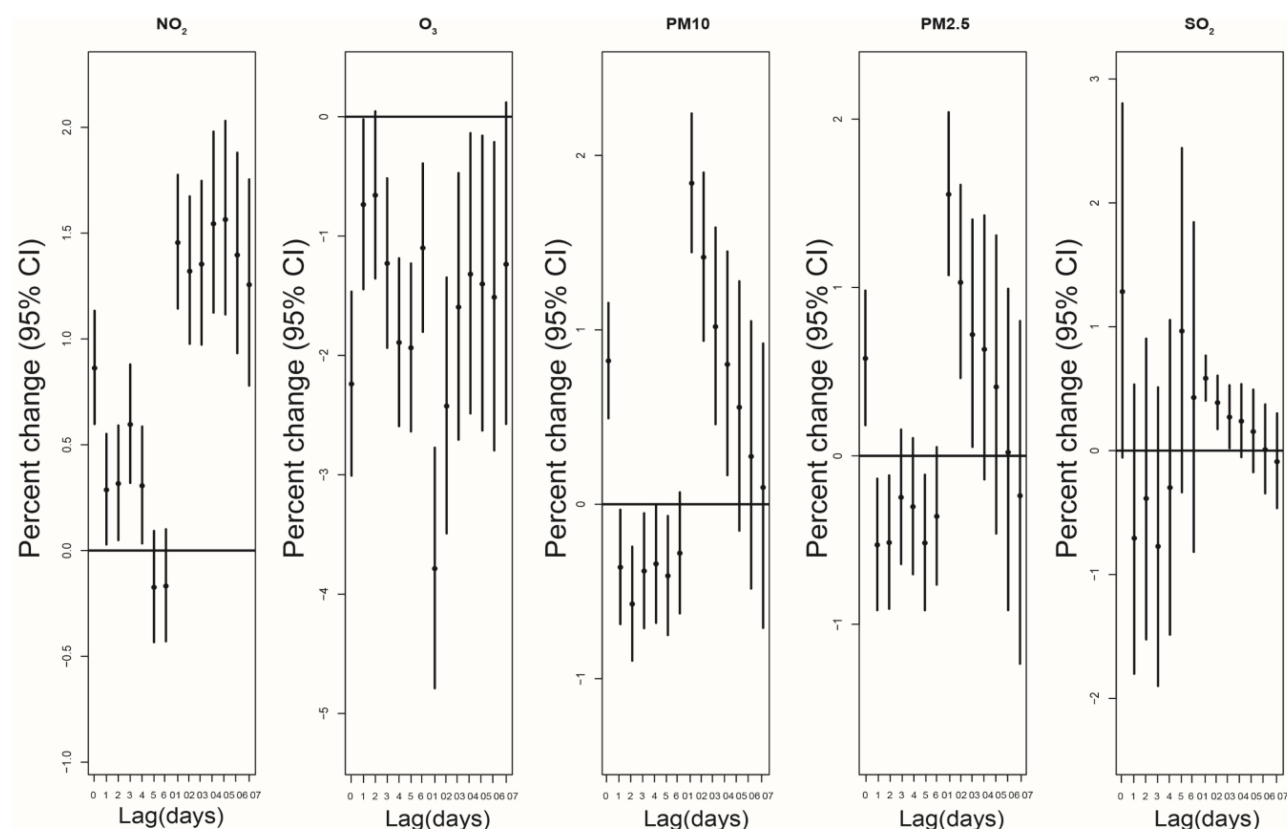
Figure 3 Percent increase of MAFLD outpatient visits cases with 10 μg/m^3 increase of NO$_2$, O$_3$, PM10, PM2.5, and SO$_2$ in different lag days.

with age, in the two age groups with 45 years as the dividing line, PM2.5 has the highest impact estimation: the older the person, the greater the impact. Regarding gender, this study shows that males are more vulnerable to air pollutants, especially PM2.5. Our study shows a significant correlation between the PM in the air and the outpatient visits for MAFLD.

Table 3 Percent Change (Mean and 95% Confidence Intervals) of Daily Outpatient Visits Associated with 10 μg/m^3 Increase of Pollutant Concentrations in Single and Two-Pollutant Models

Pollutant	Two-Pollutant Models	Estimates
NO$_2$	Without adjustment	**1.53 (0.72,2.34)**
	Adjusted for O$_3$	**1.96(1.04,2.88)**
	Adjusted for SO$_2$	**1.49(0.71,2.26)**
O$_3$	Without adjustment	−1.53(−3.73,0.67)
	Adjusted for PM$_{2.5}$	−1.74(−2.74,-0.74)
	Adjusted for PM$_{10}$	−1.34(−1.74,-1.04)
	Adjusted for SO$_2$	−2.16(−4.86,0.54)
	Adjusted for NO$_2$	−1.61(−2.27,0.95)
PM10	Without adjustment	**0.31(0.14,0.49)**
	Adjusted for O$_3$	**1.35(1.28,1.42)**
PM2.5	Without adjustment	**1.60(1.13,2.07)**
	Adjusted for O$_3$	**1.87(1.25,2.46)**
	Adjusted for SO$_2$	**3.45(1.34,5.56)**
SO$_2$	Without adjustment	4.29(−3.58,12.16)
	Adjusted for PM$_{2.5}$	3.71(−1.15,8.57)
	Adjusted for NO$_2$	2.34(−0.45,5.13)
	Adjusted for O$_3$	−2.34(−4.56,0.13)

Note: Significant statistical estimates are highlighted in bold.

With regard to the pathogenesis of MAFLD, inflammation and oxidative stress caused by the metabolic syndrome are widely considered as the key factors in the pathogenesis of nonalcoholic fatty liver disease.[23] In addition, many studies showed that the systemic proinflammatory and oxidative responses induced by air pollutants are associated with the metabolic syndrome.[24–27] Therefore, it can be concluded that air pollutants are related to the pathogenesis of MAFLD. Our findings are consistent with this conclusion. In addition to oxidative stress, the activation of Kupffer cells and macrophages, as well as the production of cytokines and chemokines, plays a central role in the progression of MAFLD. Studies have shown that the particles in the air enter the circulation through the alveolar membrane and reach the liver; these fine particles in circulation can then accumulate in the Kupffer cells and induce the secretion of cytokines in Kupffer cells, in turn leading to inflammation and collagen synthesis in hepatic stellate cells.[28,29] This study suggests that there are gender differences in the effects of air pollutants on fatty liver disease. Relevant studies indicate that this gender difference can be attributed to the differences in biological characteristics, such as sex hormone levels, body size, lung size, and growth, which may affect the biological transport of environment-derived chemicals.[30]

In addition, studies have shown that lifestyle such as physical activity patterns and dietary intake may also lead to gender-specific air pollution effects. Compared with girls, boys are more likely to engage in outdoor sports and take in more solid substances,[31] and boys participate in more moderate-to-intense sports activities.[32] This difference may cause boys to be more vulnerable to air pollution exposure than girls. Regarding the differences in age, previous studies have shown that the elderly are more vulnerable to air pollution than younger people.[33,34] However, some studies have reported, that compared with the elderly, young people may be more prone to lipid metabolism disorders.[35] In addition, we did not find relevant literature to explain the mechanism of age in the effect of air pollutants on MAFLD; therefore, our conclusion that "the older the age, the greater the impact of air pollutants" should be verified in a larger sample.

This study has some limitations. Potential confounding factors such as body mass index, education level, smoking habits, and drug use history may also have an impact on the relationship between air pollutants and fatty liver disease. Second, we only collected the daily number of outpatient visits from one hospital, which may not represent the overall level of the city.

Conclusion

This study concluded that the number of outpatient visits for MAFLD is related to air pollution exposure. The effects of different air pollutants on MAFLD outpatient visits were different in different seasons, ages, and genders. It suggests that sufficient health counseling about hot temperature exposure and transition seasons should be included in care programs for patients with MAFLD.

Data Sharing Statement

The original data are available on request to Ming-Wei Wang, or at the Affiliated Hospital of Hangzhou Normal University, Hangzhou, 310014, China.

Consent for Publication

Not applicable. All data were supplied and analysed in an anonymous format, without access to personal identifying information.

Acknowledgment

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or critically revising it for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare that there is no conflict of interests regarding the publication of this paper.

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