Effect of Air Pollution on Metabolism-Associated Fatty Liver Disease: A Hospital-Based Study

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Effect of air pollution on metabolism-associated fatty liver disease: A hospital-based study

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List of Abbreviations:

MAFLD-metabolism-associated fatty liver disease; NFLD-nonalcoholic fatty liver disease; T2DM-type 2 diabetes mellitus; DEP-diesel exhaust particulates ;PM- particulate matter ,O₃ – ozone; NO₂-nitrogen dioxide;SO₂ -and sulfur dioxide ;

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Abstract:

Background Many studies have shown that the fine particulate matter in air is related to the incidence rate of chronic diseases. However, research on air pollution and metabolism-associated fatty liver disease (MAFLD) is limited. The purpose of this study was to explore the relationship between the incidence rate of MAFLD and air pollutants.

Methods using a quasi-Poisson regression generalized additive model. Stratified analyses by season and age were also performed.

Results A 10 $\mu\text{g}/\text{m}^3$ increase of PM₁₀, PM_{2.5}, and NO₂ concentrations corresponded to 0.82 (95%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. In terms of season, the impact estimates of NO₂ and PM_{2.5} 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 warm season, the impact estimates of PM₁₀ were more significant in the cool season: 2.88 (95% CI, 0.66-5.10). NO₂ has the highest effect in the transition season, while PM₁₀ has the highest effect in the cool and hot seasons. In the two age groups with 45 years as the dividing line, PM_{2.5} has the highest impact estimate: 2.69 (95% CI, 0.77-5.61) and 2.88 (95% CI, 0.37-6.40). The impact values of PM_{2.5} in male and Female were 3.60 (95% CI, 0.63-6.57) and 1.65 (95% CI, 1.05-2.25), respectively. The most important link is in different lag models, there is a significant correlation.

Conclusion: This study shows that the air pollutants are related to the incidence rate of MAFLD. The effects of different air pollutants on MAFLD incidence rate were different in different seasons, ages, and gender. It is found that air pollution has a lag effect on MAFLD.

Key words: Air pollutants, metabolism-associated fatty liver disease, time-series study

1.Introduction

Metabolism-associated fatty liver disease (MAFLD) (formerly known as nonalcoholic fatty liver disease (NFLD)) 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 (T2DM), or metabolic dysfunction, such as waist circumference and dyslipidemia or hyperglycemia(1). Studies have shown that the prevalence of MAFLD has increased to a worrying level, bringing a huge burden on individuals and the health care system(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 the rapid change 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% from 2016 to 2030, reaching 3145.8 million cases(1).

According to the analysis of WHO on the disease burden caused by air pollution, more than two million premature deaths each year can be attributed to urban outdoor and indoor air pollution(5). Four common air pollutants include particulate matter (PM), ozone (O₃), nitrogen dioxide (NO₂), and sulfur dioxide (SO₂) (6). The global burden of disease study identified air pollution as the main cause of global burden of disease, especially in developing countries(7-8) . Studies have shown that air pollution not only affects respiratory diseases, but also affects acute myocardial infarction, arrhythmia, conjunctivitis, and mental disorders (9-12).

Besides, studies have shown that long-term exposure to PM_{2.5}, PM₁₀, and NO₂ is positively associated with the prevalence of metabolic syndrome in children and adolescents

(13-15). More and more evidence shows that environmental pollutants such as diesel exhaust particulates (DEP), suspended PM, metals, and polychlorinated compounds are important risk factors for the development of NFLD (16). According to the research of Giovanni Tarantino et al., exposure to ambient air particles with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ (PM_{2.5}) can enhance NFLD. Therefore, the effect of environmental factors on liver disease has attracted much attention(17). up to now, some studies on the relationship between fatty liver disease and air pollution have been conducted in animals (18-20). Therefore, in this study we performed a time series was used to analyze the relationship between short-term air pollution exposure and fatty liver disease based on the cases of Affiliated Hospital of Hangzhou Normal University in Hangzhou.

2. Materials and methods

Air pollution and meteorological data

Air quality monitoring stations are located in Hangzhou, providing daily values of PM_{2.5} ($\mu\text{g}/\text{m}^3$), PM₁₀ ($\mu\text{g}/\text{m}^3$), SO₂ ($\mu\text{g}/\text{m}^3$), O₃ ($\mu\text{g}/\text{m}^3$), NO₂ ($\mu\text{g}/\text{m}^3$), CO ($\mu\text{g}/\text{m}^3$), relative humidity (%), and mean temperature ($^{\circ}\text{C}$). The details of Affiliated Hospital of Hangzhou Normal University and specific air quality monitoring stations are shown in Appendix 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-h averages, and the O₃ concentration was the maximal 8-h average from all valid monitoring sites in this study.

Hospital case data

The data of MAFLD from January 2017 to August 2019 were collected from the outpatient database of Affiliated Hospital of Hangzhou Normal University. Patients diagnosed with MAFLD were included in this study. The diagnosis of MAFLD 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, T2DM, or metabolic dysfunction, such as waist circumference and dyslipidemia or hyperglycemia (Eslam et al., 2020). In this study, 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 patients with MAFLD were enrolled. The ethics committee of Affiliated Hospital of Hangzhou Normal University approved all the procedures performed in this study.

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 (Yang et al., 2014). Briefly, the following log-linear GAM was fitted to obtain the estimated pollution log-relative rate β in the selected city:

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

where $E(Y_t)$ is the expected number of MAFLD cases 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 (22).

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 cases per 10 $\mu\text{g}/\text{m}^3$ 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.

3. Results

The basic descriptive statistics of the number of cases, pollutants, and meteorological data are shown in Table 1. From January 1, 2017 to August 31, 2019, 10,562 confirmed cases 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 and Transition seasons. During the study period, the daily average concentrations of NO_2 , SO_2 , PM_{10} , O_3 , and $\text{PM}_{2.5}$ were 48.43 $\mu\text{g}/\text{m}^3$, 35.89 $\mu\text{g}/\text{m}^3$, 56.80 $\mu\text{g}/\text{m}^3$, 137.50 $\mu\text{g}/\text{m}^3$, and 48.91 $\mu\text{g}/\text{m}^3$, respectively. The daily average humidity and temperature were 75.21% and 18.45 $^{\circ}\text{C}$, respectively.

Fig. 1 shows significant differences among the five different air pollution indicators and number of cases in three different seasons. The daily air pollution concentration and the number of MAFLD cases (except O_3) are the highest in the cool season and the lowest in the hot season. The number of cases is the most in hot seasons. The Spearman correlation coefficients of $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 were 0.68-0.95. The maximum 8-h mean O_3 concentration negatively correlated with $\text{PM}_{2.5}$, PM_{10} , SO_2 , and NO_2 (Spearman correlation coefficient ranged from -0.27 to -0.06) (Fig. 2).

According to Table 2, in terms of seasons, the effect of ambient air pollution on the total number of cases with MAFLD shows significant differences among the three seasons. The impact estimates of NO_2 and $\text{PM}_{2.5}$ 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 PM_{10} were more significant in the cool season: 2.88 (95% CI, 0.66-5.10). NO_2 has the highest effect in the transition season, while PM_{10} has the highest effect in the cool and hot seasons. Regarding age, the study shows an increase in the correlation percentage between NO_2 , PM_{10} , $\text{PM}_{2.5}$, and the total number of outpatients with MAFLD varies with

age groups. The older the age, the higher the impact estimate. In the two age groups with 45 years as the dividing line, PM_{2.5} 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 female, NO₂, PM₁₀, and PM_{2.5} had a greater impact on male, especially PM_{2.5}. The impact values of PM_{2.5} in male and female were 3.60 (95% CI, 0.63-6.57) and 1.65 (95% CI, 1.05-2.25), respectively.

Fig. 3 shows the results obtained from the single-lag day (lag0–lag6) and cumulative exposure models (lag01–lag07) for the percent increase in MAFLD outpatients per 10 µg/m³ increase in pollutants. Statistically significant results were observed at lag 0–4 and 01–07 day for NO₂, Lag 0 and 01–04 day for PM₁₀, Lag 0 and 01–03 day for PM_{2.5}, and Lag 01-03 day for SO₂. 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 NO₂, PM₁₀, and PM_{2.5} pollutants remained statistically significant when adjusting for co-pollutants.

4. Discussion

This study shows that the air pollutants in Hangzhou are related to the incidence rate of MAFLD. The effects of different air pollutants on MAFLD incidence rate were different in different seasons, ages, and gender. The most significant associations of air pollution appeared on single days and the associations in the cumulative exposure models were still positive. Regarding seasonal aspect, NO₂ showed the highest effect in the transition season, while PM₁₀ had the highest effect in the cool and hot seasons. The effect of PM₁₀ was more significant in the cool season. Regarding age aspect, in the two age groups with 45 years as the dividing line, PM_{2.5} has the highest impact estimation: the older the person, the greater the impact. Regarding gender, this study shows that male are more vulnerable to air pollutants, especially PM_{2.5}. Our study shows a significant correlation between the PM in the air and the incidence rate of MAFLD.

With regard to the pathogenesis of MAFLD, inflammation and oxidative stress caused by metabolic syndrome are widely considered as the key factors in the pathogenesis of NFLD (23). Besides, many studies showed that the systemic proinflammatory and oxidative responses induced by air pollutants are associated with metabolic syndrome (24). Therefore, it can be concluded that air pollutants are related to the pathogenesis of MAFLD. Our conclusion is consistent with this conclusion. Besides oxidative stress, activation of Kupffer cells/macrophages, and production of cytokines/chemokines play a central role in the progression of MAFLD (25). Studies have shown that the particles in the air enter the circulation through the alveolar membrane and reach the liver; the fine particles in the 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 (24,26). This study suggests 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 (27).

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 (13,27); besides, boys participate in more moderate-to-intense sports activities (13,27,28). This may cause boys

to be more vulnerable to air pollution exposure than girls. Regarding the difference in age, previous studies have shown that the elderly people are more vulnerable to air pollution than the young people(12,29,30); however, some studies have reported that compared with the elderly people, young people may be more prone to lipid metabolism disorders (31). 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 by increasing the sample size.

However, this study has some limitations. Potential confounding factors such as the body mass index, education level, smoking habits, and drug use history may also have a potential impact on the relationship between air pollutants and fatty liver disease. Second, we only collected the daily number of cases from one hospital, which may not represent the overall level of the city. Therefore, we can further expand the number of cases and environmental factors to further support our findings.

5.Conclusion:

In conclusion, this study concluded that MAFLD is related to air pollution exposure. The effects of different air pollutants on MAFLD incidence rate were different in different seasons, ages, and gender. It suggests that sufficient health counseling about hot temperature exposure and cooling measures in summer should be included in care programs for MAFLD patients.

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Availability of data and materials

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

Conflict of interests

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

Consent for publication

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

Author contributions

YRC, ZHF conceived the study and designed the analysis, YRC and NW performed statistical analysis, MWW and WW wrote the first draft of the manuscript, MYZ, JN, JJ ,CYW and WXX

Participate in revision the manuscript, and all other authors contributed to revision of the manuscript.

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Figure Legends

Fig. 1. Box plots of five air pollutants in the cool, transition, warm seasons and 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.

Fig. 2. NO₂, O₃, PM10, PM2.5, and SO₂ 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)

Fig. 3. Percent increase of MAFLD cases with 10 µg/m³ increase of NO₂, O₃, PM10, PM2.5, and SO₂ in different lag days.

Appendix S1: The air quality monitoring point is near the Affiliated Hospital of Hangzhou Normal University

Figures

Figure 1

Box plots of five air pollutants in the cool, transition, warm seasons and 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.

Figure 2

NO₂, O₃, PM₁₀, PM_{2.5}, and SO₂ 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)

Figure 3

Percent increase of MAFLD cases with 10 $\mu\text{g}/\text{m}^3$ increase of NO₂, O₃, PM₁₀, PM_{2.5}, and SO₂ in different lag days. Appendix S1: The air quality monitoring point is near the Affiliated Hospital of Hangzhou Normal University

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