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Short-term exposure to air pollution on peripheral white blood cells and inflammation biomarkers: a cross-sectional study on rural residents

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Abstract

Effects of short-term exposure to ambient air pollution on systemic immunological and inflammatory biomarkers in rural population have not been adequately characterized. From May to July 2021, 5816 participants in rural villages of northern Henan Province, China, participated in this cross-sectional study. Blood biomarkers of systemic inflammation were determined including peripheral white blood cells (WBC), eosinophils (EOS), basophils (BAS), monocytes (MON), lymphocytes (LYM), neutrophils (NEU), neutrophil-lymphocyte ratio (NLR), and serum high-sensitivity C-reactive protein (hs-CRP). The concentrations of ambient fine particulate matter (PM_{2.5}), PM₁₀, nitrogen dioxide (NO₂), carbon monoxide (CO), and ozone (O₃) were assessed up to 7 days prior to the blood draw. A generalized linear model was used to analyze the associations between air pollution exposure and the above-mentioned blood biomarkers. Significantly positive associations were revealed between PM_{2.5}, CO and WBC; CO, O₃ and LYM; PM_{2.5}, PM₁₀, SO₂, CO and NEU; PM_{2.5}, PM₁₀, SO₂, CO and NLR; PM_{2.5}, PM₁₀, SO₂, NO₂, CO, O₃ and hs-CRP. Meanwhile, negative associations were found between SO₂ and WBC; PM_{2.5}, PM₁₀, NO₂, CO, or O₃ and EOS; PM_{2.5}, SO₂, or CO and BAS; SO₂, NO₂ or O₃ and MON; PM_{2.5}, PM₁₀, SO₂, or NO₂ and LYM. Moreover, men, individuals with normal body mass index (BMI), current smokers, and those older than 60 years were found vulnerable to air pollution effects. Taken together, short-term exposure to air pollution was associated with systemic inflammatory responses, providing insight into the potential mechanisms for air pollution-induced detrimental systemic effects in rural residents.

Keywords Air pollution, Inflammation, Cross-sectional study, Neutrophil-lymphocyte ratio

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Introduction

Air pollution is a major environmental threat to human health worldwide and has been shown to be associated with a wide range of adverse health outcomes. Previous epidemiological studies have shown that exposure to air pollution leads to a variety of adverse health outcomes, including cardiorespiratory and autoimmune diseases, and can even increase mortality in the population [1–4]. Many pathophysiological alterations, such as inflammation, oxidative stress, and immunological disorders, have been attributed to air pollution exposure [5, 6]. Documented studies have indicated that air pollutants are capable of stimulating airway epithelial cells and immune cells, resulting in airway epithelial damage and detrimental effects beyond the lung, including systemic immunological and inflammatory responses [7–10].

One of the primary systemic inflammatory responses is the stimulation of the haematopoietic system to release leukocytes and platelets into the circulation. Previous studies have shown that leukocytes are a reliable predictor for air pollution-induced short- and long-term health effects [11–13]. Epidemiological investigations have discovered the relationships between short-term exposure to ambient air pollutants and the alterations of peripheral white blood cells in urban populations, such as peripheral white blood cells (WBC), eosinophils (EOS), basophils (BAS), monocytes (MON), lymphocytes (LYM), and neutrophils (NEU), neutrophil/lymphocyte ratio (NLR) [13–15]. In particular, NLR responds to the dynamic changes in neutrophils and lymphocytes and can be applied to quantify the dynamic action of cellular innate and adaptive immune responses, being considered as a new perspective marker of and a valid indicator of systemic inflammation [16–18]. Thus far, the association of short-term air pollution exposure with NLR has been less characterized, with no evidence available for rural populations. In addition, high-sensitivity C-reactive protein (hs-CRP), a simple, rapid and cost-effective biomarker of systemic inflammation [18], has been widely utilized to assess health effects of short-term air pollution exposure due to its high sensitivity, but the existing evidence appears inconsistent [19–21].

Xinxiang is located north of Henan province, one of the most populous provinces and the top region by rural population in China, and is one of the regions in the country with severe air pollution [22]. Noteworthy, the population in this present study was living in a typical and modern rural area with traditional agriculture and community-managed industries. This represents the new trend of village development (rural revitalization) in modern China. Thus, the findings from this study could apply to other rural areas in Henan province or part of other provinces. Therefore, it is of practical significance to evaluate health consequences of air pollution

on rural dwellers in this developing regions. Given that systemic inflammation is a common and essential event in the pathogenesis of many diseases, examination of blood biomarkers for systemic inflammation is crucial to identify early alterations of adverse health effects and take measures to prevent progression of diverse non-communicable chronic diseases. It should also be noted that examination of white blood cells as well as soluble biomarkers of systemic inflammation was an indispensable part of the funded national project which supported this present study. In this context, the aim of this present study was to evaluate the effects of short-term exposure to ambient air pollution on peripheral white blood cells and serum biomarker for systemic inflammation in the rural population of Xinxiang, and to provide clues for design of preventive and therapeutic strategies.

Methods

Study participants

5816 participants were finally recruited in rural villages of Xinxiang from May to July 2021. Trained investigators employed standardized questionnaires to gather individual data, such as demographic characteristics, lifestyle habits, and disease history. Smoking, drinking, and physical activities were specified as previously reported [23]. Herein, smoking was defined as a minimum of one cigarette a day for more than 6 months; drinking as consuming alcohol 12 or more times annually, and physical activity levels as high, moderate, and low based on the physical activity-metabolic equivalent. The disease status of the participants was designated by the Charlson Comorbidity Index (CCI) [24]. Body mass index (BMI) was calculated as the ratio of body weight in kilograms(kg) divided by the square of height in meters (m^2). The Ethics Committee of Xinxiang Medical University for Human Studies authorized this investigation (XYLL-2,016,242). Moreover, the informed consent was given willingly and in writing by each participant.

Estimation of air pollution exposures

Ambient air pollutant concentrations included the 24-h average concentrations of $PM_{2.5}$ (particulate matter with a diameter of 2.5 μm and less), PM_{10} , nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and the daily maximum 8-h average concentrations of ozone (O_3) from May 26 to July 20, 2021, were obtained from Xinxiang Environmental Monitoring Station. The distance between the participant's dwellings and the environmental monitoring site was less than 10 km. The daily average temperature and relative humidity was obtained from the China Meteorological Data Network. In addition to single-day lag models (lag0 to lag7), moving average lag models (lag01 and lag07) were also used to assess the impacts of air pollution exposure.

Measurements of peripheral blood biomarkers

15.0 ml peripheral venous blood was drawn by medical staff from each participant fasting for at least 8 h. 10.0 ml of blood was put into an anticoagulant-treated tube and gently mixed before cell counting. The other 5.0 ml of blood was drained into a tube without anticoagulant treatment and sat for 30–60 min at room temperature to collect serum for hs-CRP measurement. WBC, EOS, BAS, MON, LYM, and NEU were counted using an automated hematology analyzer (XS-500i, Sysmex Corporation, Kobe, Japan) and NLR calculated. Serum hs-CRP was measured using an automated clinical chemistry analyzer (CS-2000, Dirui Industrial, China). The biomarkers were examined by a certified clinical laboratory with standardized operating and quality control procedures.

Statistical analyses

Continuous variables' normal and non-normal distributions were presented, respectively, as mean (standard deviation) and median (interquartile range); categorical variables were expressed as number (percentage).

The association between exposure to air pollution and meteorological factors were assessed by Spearman correlation analyses. The short-term impact of ambient air pollution on blood biomarkers was evaluated using multivariable linear regression models. To assess the lag-associated effects of air pollution exposure, the model incorporated a spectrum of lagged, including single-day lags and moving averages of multiple lagged days (lag0–7, 01–07). Blood biomarker values were normalized using log₁₀ transformation before being included into the models. Those estimated effects were displayed as a percentage change (95% CI) for every 10 $\mu\text{g}/\text{m}^3$ increasing concentration of each air pollutant.

For each air pollutant, its effect on a single biomarker was evaluated individually. The air pollution exposure model was adjusted for age, BMI, and category-type variables including sex, villages, marital, smoking and drinking status, education, average monthly income, and physical activity levels, CCI, allergy, and meteorological factors including temperature and relative humidity. For the latter, only those lag dates that produced minimum moving average values of Akaike Information Criterion (AIC) were selected.

To investigate the confounding effects of sex (male vs. female), BMI (<24 vs. ≥ 24 kg/m^2), smoking status (current smoker, never or former smokers), and age (≥ 60 vs. < 60 years) on the relationship between air pollution exposure and blood biomarkers, stratification analyses were preformed. To verify the robustness of the estimated effects and allow for the adjustment of co-pollutants, sensitivity analyses were carried out with two-pollutant models.

R software (version 4.1.3) was used for all data analyses, and the “ggplot2” package was used to visualize data. The threshold for statistical significance was set at $P < 0.05$.

Results

Demographic characteristics of the participants

Demographic characteristics and blood biomarkers of the participants are presented in Table 1. In this study, 2157 males (37.1%) and 3659 females (62.9%) with an average age of 57.79 years and BMI of 25.59 kg/m^2 were recruited. Of 5816 subjects, 16.5% were current smokers and 77.6% former smokers; 63.8% had high physical activity and 31.5% moderate activity. The median counts for WBC, EOS, BAS, MON, LYM, and NEU were $5.97 \times 10^9/\text{L}$, $0.09 \times 10^9/\text{L}$, $0.03 \times 10^9/\text{L}$, $0.27 \times 10^9/\text{L}$, $1.98 \times 10^9/\text{L}$, and $3.48 \times 10^9/\text{L}$, respectively, and the median of NLR was 1.7%. Meanwhile, the mean serum level of hs-CRP was 2.04 mg/L .

Correlations of ambient air pollutants and meteorological variables

Table 2 shows the distribution of air pollutant concentrations and meteorological variables over the survey period. The median levels of $\text{PM}_{2.5}$, PM_{10} , SO_2 , NO_2 , O_3 , and CO were 24.50 (8.0–65.0), 56.50 (20.0–148.0), 10.00 (2.0–16.0), 19.00 (7.0–37.0), 86.00 (39.6–68.0) $\mu\text{g}/\text{m}^3$ and 0.60 (0.3–1.3) $\mu\text{g}/\text{m}^3$, respectively. $\text{PM}_{2.5}$ and PM_{10} concentrations were above the current World Health Organization's air quality guidelines. In addition, the median temperature and relative humidity were 28.10 (23.3–31.7) $^\circ\text{C}$ and 64.5 (26–100) %, respectively.

The associations of air pollutant concentrations with meteorological factors were assessed with Spearman correlation analyses. The varied correlations were shown in Fig. S1.

Effects of air pollution exposure on blood biomarkers

After adjustment for confounding factors, the associations between air pollutant levels and blood cellular biomarkers are depicted in Fig. 1.

As shown in Fig. 1, exposure to $\text{PM}_{2.5}$ (lag5, lag6) or CO (lag5, lag6, lag06, and lag07) was positively correlated to total WBC counts, respectively. Every 10 $\mu\text{g}/\text{m}^3$ increment in $\text{PM}_{2.5}$ (lag5) and CO (lag07) was related to 0.51% (95% CI: 0.19%, 0.82%) and 0.04% (95% CI: 0.01%, 0.07%) increase in total WBC counts, respectively. In contrast, SO_2 exposure was negatively correlated with this parameter, each 10 $\mu\text{g}/\text{m}^3$ increase in SO_2 (lag5) was negatively associated with -1.34% (95% CI: -0.08% , -2.6%) decrease in WBC counts. No correlations were detected between PM_{10} , NO_2 , or O_3 exposure with WBC count.

In addition, Fig. 1 also shows the associations of air pollution exposures with EOS counts. Exposures to $\text{PM}_{2.5}$ (lag1, 6, 7, 03–07), PM_{10} (lag1, 3, 6, 02–07), NO_2

Table 1 Descriptive characteristics and blood biomarkers of the participants

Characteristics	Total (5816)
Age, years (SD)	57.79 (12.62)
BMI (SD)	25.59 (3.63)
Sex, n (%)	
Male	2157 (37.1)
Female	3659 (62.9)
Villages, n (%)	
Lang Gongmiao	3097 (53.2)
Qi Liying	2608 (44.8)
Others	111 (2.0)
Marital status, n (%)	
Married/cohabiting	5169 (88.9)
Unmarried/separated/divorced	647 (11.1)
Educational levels, n (%)	
Elementary school or below	2050 (35.2)
Middle school	2277 (39.2)
High school or above	1489 (25.6)
Average monthly income, n (%)	
<500 RMB	1509 (25.9)
500–900 RMB	1734 (29.8)
>500 RMB	2573 (44.2)
Smoking, n (%)	
Never	4515 (77.6)
Current	960 (16.5)
Former	341 (5.9)
Drinking, n (%)	
Never	4681 (80.5)
Current	914 (15.7)
Former	221 (3.8)
Physical activity, n (%)	
Low	276 (4.7)
Moderate	3709 (63.8)
High	1831 (31.5)
CCI, n (%)	
0-level	2476 (42.6)
1-level	1705 (29.3)
2-level	900 (15.5)
3-level	735 (12.6)
Allergy, n (%)	
Yes	776 (13.3)
No	5040(86.7)
Total WBC ($\times 10^9/L$), median (IQR)	5.97 (2.05)
EOS ($\times 10^9/L$), median (IQR)	0.09 (0.09)
BAS ($\times 10^9/L$), median (IQR)	0.03 (0.03)
MON ($\times 10^9/L$), median (IQR)	0.27 (0.10)
LYM ($\times 10^9/L$), median (IQR)	1.98 (0.77)
NEU ($\times 10^9/L$), median (IQR)	3.48 (1.53)
NLR (%), median (IQR)	1.74 (0.88)
hs-CRP (mg/L), median (IQR)	2.04 (1.92)

Abbreviations WBC, white blood cells; EOS, eosinophils; BAS, basophils; MON, monocytes; LYM, lymphocytes; and neutrophils (NEU); hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-lymphocyte ratio; SD, standard deviation; IQR, interquartile

Table 2 Summary statistics for air pollutant concentrations and meteorological variables during the study period

Variable	Minimum	Percentile			Maximum
		25th	50th	75th	
PM _{2.5} (ug/m ³)	8.00	17.75	24.50	35.25	65.00
PM ₁₀ (ug/m ³)	20.00	46.00	56.50	95.50	148.00
SO ₂ (ug/m ³)	2.00	9.00	10.00	12.00	16.00
NO ₂ (ug/m ³)	7.00	13.00	19.00	25.00	37.00
CO (mg/m ³)	0.30	0.40	0.60	0.70	1.30
O ₃ (ug/m ³)	39.00	66.00	86.00	106.00	168.00
T (°C)	23.20	26.03	28.10	29.18	31.70
RH (%)	26.00	50.50	64.50	79.50	100.00

(lag7), CO (lag7) and O₃ (lag1, 6), but not for SO₂ exposure, were negatively associated with EOS counts. The strongest effects on EOS was seen with PM_{2.5} (lag07), PM₁₀ (07), NO₂ (lag7), CO (lag7), and O₃ (lag1) exposures. Each 10 $\mu\text{g}/\text{m}^3$ rise in PM_{2.5}, PM₁₀, NO₂, CO, and O₃ levels under these exposure scenarios was related to a decrease of -2.99% (95 CI: -0.99%, -5%), -1.08% (95 CI: -0.29%, -1.88%), -2.48% (95 CI: -0.85%, -4.12%), -0.07% (95 CI: -0.01%, -0.12%) and -0.38% (95 CI: -0.04%, -0.73%) in EOS, respectively.

The negative effects of air pollution on BAS were also detected as for EOS. Each 10 $\mu\text{g}/\text{m}^3$ increment in PM_{2.5}, SO₂ and CO concentrations was related to a decline of -0.65% (95% CI: 0.00%, -1.30%), -2.22% (95% CI: -0.03%, -4.40%), and -0.04% (95% CI: 0.00%, -0.08%) in BAS (lag1), respectively. The decreasing trends for BAS count following PM₁₀ and NO₂ exposure were observed, but not significant.

Short-term exposure to SO₂, NO₂, or O₃ posed negative effect on MON count. Each 10 $\mu\text{g}/\text{m}^3$ increase in SO₂ (lag5), NO₂ (lag7), and O₃ (lag04) was associated with a decrease of -1.61% (95% CI: -0.28%, -2.94%), -0.89% (95% CI: -0.27%, -1.51%) and -0.31% (95% CI: 0.08%, -0.54%) in MON count, respectively. Nevertheless, there was no significant associations between PM_{2.5}, PM₁₀, or CO levels and MON count.

The concentrations of PM_{2.5} (lag1, 7), PM₁₀ (lag1-3, lag6 and lag01-07), SO₂ (lag7, lag07) and NO₂ (lag7) were negatively associated with LYM count, while CO (lag0, 5) and O₃ (lag0, 4) were positively related to this parameter. And the largest estimated effects on LYM for the aforementioned air pollutants were observed with PM_{2.5} (lag1) (-0.39% CI: -0.02, -0.76), PM₁₀ (lag07) (-0.59%, 95% CI: -0.23%, -0.95%), SO₂ (lag07) (-5.54%, 95% CI: -1.53%, -9.56%), NO₂ (lag7) (-0.90%, 95% CI: -0.14%, -1.66%), CO (lag0) (0.03%, 95% CI: 0.01%, 0.05%), or O₃ (lag4) (0.15%, 95% CI: 0.04%, 0.27%).

There existed significantly positive associations of PM_{2.5} (lag5-7, lag06-07), PM₁₀ (lag7), SO₂ (lag7), or CO (lag2,5-7, lag 05-07) exposure with NEU count, respectively. The maximum effects of air pollution exposure on

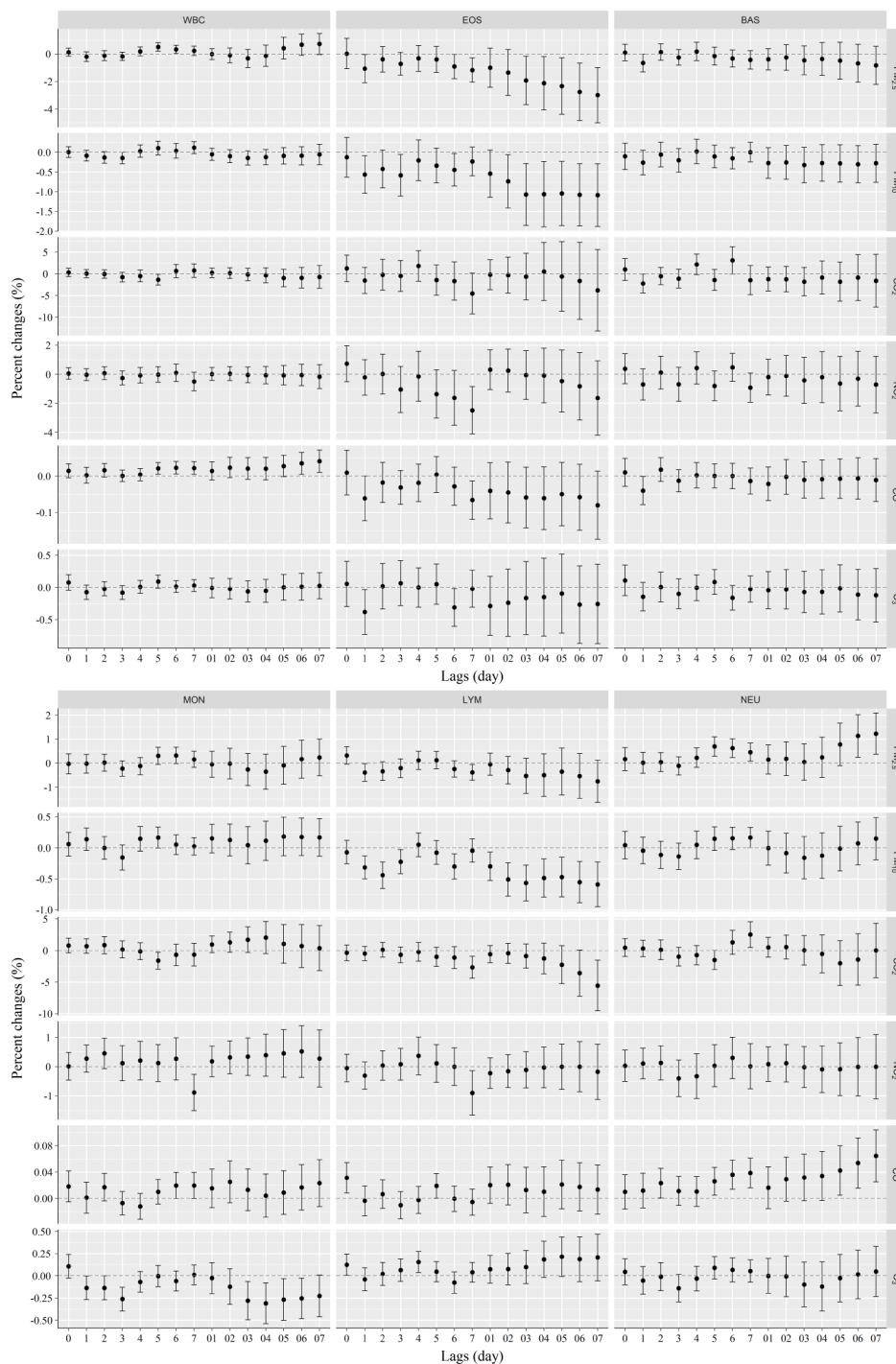


Fig. 1 Association of short-term exposure to air pollutants with WBC and subtypes at different lags. The effects were presented as percentage changes (%) per 10 $\mu\text{g}/\text{m}^3$ changes in air pollutant concentrations. *Abbreviations* WBC, white blood cells; EOS, eosinophils; BAS, basophils; MON, monocytes; LYM, lymphocytes; NEU, neutrophils

NEU count occurred with $\text{PM}_{2.5}$ (lag07), PM_{10} (lag7), SO_2 (lag7), or CO (lag07). Under this circumstance, each 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, PM_{10} , SO_2 , and CO correlated to an increase of 1.23% (95%CI: 0.37%, 2.09%), 0.17%

(95%CI: 0.00%, 0.33%), 2.51% (95%CI: 0.48%, 4.54%), and 0.06% (95%CI: 0.03%, 0.1%) in NEU count.

As illustrated in Fig. 2, significantly positive associations were revealed between $\text{PM}_{2.5}$ (lag1, 5–7, lag05–07), PM_{10} (lag1, 5, 6, lag 02, 05–07), SO_2 (lag6, lag7), or CO

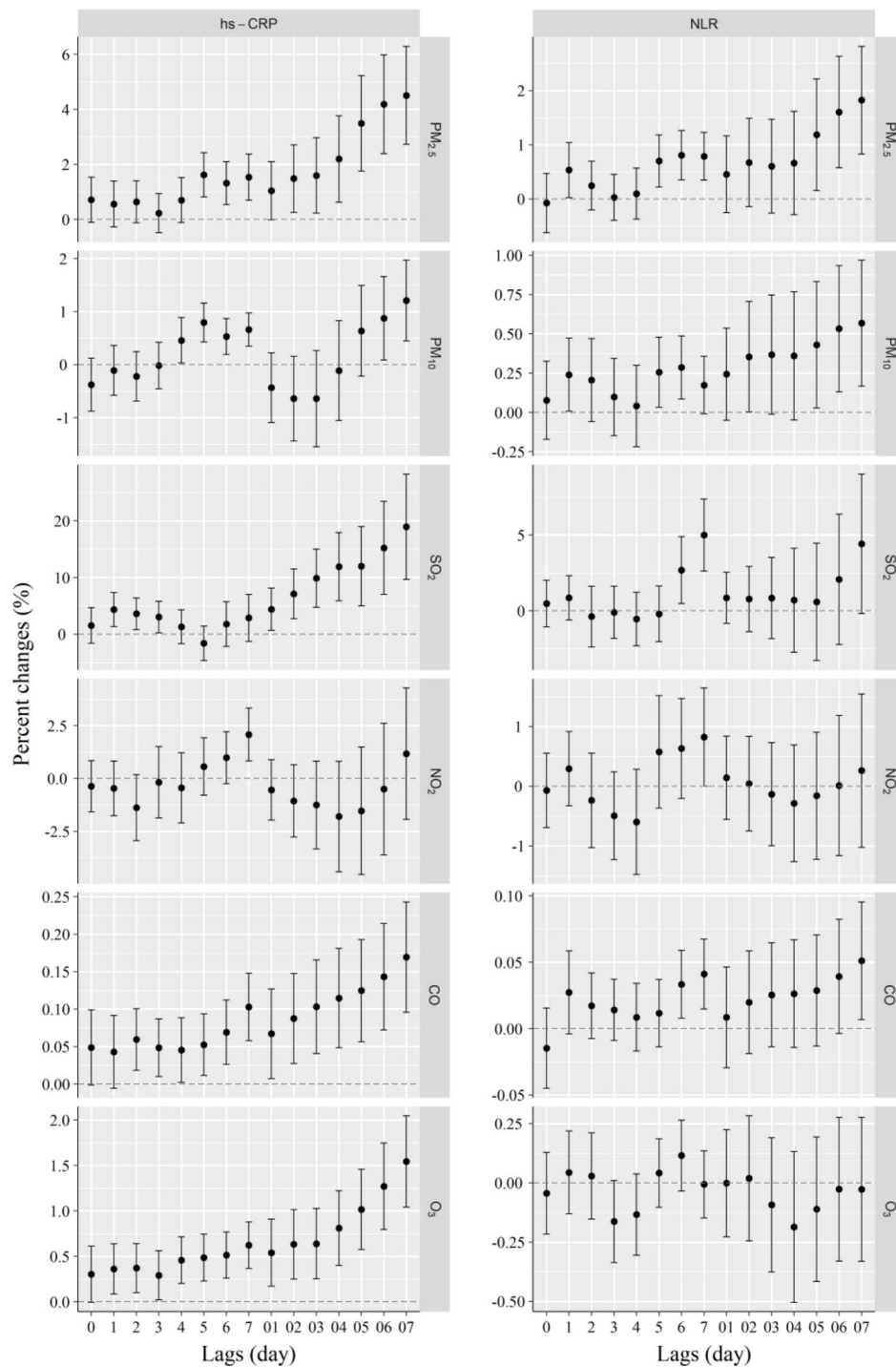


Fig. 2 Association of short-term exposure to air pollutants with NLR and hs-CRP at different lags. The effects were represented as percentage changes (%) for each 10 $\mu\text{g}/\text{m}^3$ changes in air pollutants concentration. *Abbreviations* NLR, neutrophil-lymphocyte ratio; hs-CRP, high-sensitivity C-reactive protein

(lag6, lag7, lag07) exposure and NLR. Moreover, $\text{PM}_{2.5}$ (lag07), PM_{10} (lag07), SO_2 (lag7), and CO (lag07) posed strongest effects, corresponding to rises in NLR of 1.82% (95%CI: 0.83%, 2.82%), 0.57% (95%CI: 0.17%, 0.97%), 4.99% (95%CI: 2.62%, 7.36%), and 0.05% (95%CI: 0.01%, 0.1%).

Short-term air pollution exposure was found to be significantly related to serum hs-CRP (Fig. 2). Specifically, $\text{PM}_{2.5}$ (lag5-7, lag02-07), PM_{10} (lag4-7, lag06, lag07), SO_2 (lag1-3, lag01-07), NO_2 (lag7), CO (lag2-7, lag01-07), and O_3 (lag1-7, lag01-07) exposures had significantly positive associations with serum levels of hs-CRP. Hs-CRP

increased by 4.51% (95%CI: 2.72%, 6.29%), 1.21% (95%CI: 0.45%, 1.97%), 18.96% (95%CI: 9.66%, 28.26%), 2.08% (95%CI: 0.83%, 3.33%), 0.17% (95%CI: 0.1%, 0.24%), and 1.54% (95%CI: 1.04%, 2.05%) for each 10 µg/m³ increase in PM_{2.5} (lag07), PM₁₀ (lag07), SO₂ (lag07), NO₂ (lag7), CO (lag07), and O₃ (lag07), respectively.

Confounding factor stratification and two-pollutant model analyses

The stratification by sex, BMI, smoking status, and age was performed. It was shown that the impacts of PM_{2.5} and SO₂ on EOS were significantly higher in males than in females, but no sex difference in NLR (Fig. 3). The effects of SO₂ on NEU and hs-CRP were significantly greater in people with a BMI less than 24 kg/m² than people with a BMI ≥ 24 kg/m². This was not seen for PM_{2.5} and PM₁₀ in those with a BMI less than 24 kg/m² (Fig. 4). Current smoking was found to strengthen SO₂-induced decrease in EOS counts than non-smoking. Additionally, the effects of PM₁₀ exposure on NLR and NEU were significantly stronger in smokers than in non-smokers (Fig. 5). Older ages (≥ 60 years) significantly increased

the effects of PM_{2.5} exposure on EOS and LYM as well as the effect of SO₂ on LYM than younger ages (< 60 years) (Fig. 6).

In the two-pollutant model analyses, significant associations were detected between PM_{2.5} and counts of WBC, NEU, and NLR, as well as serum levels of hs-CRP after controlling other co-pollutants. In addition, although the significant association of PM_{2.5} with EOS or BAS became insignificant after inclusion of PM₁₀ or SO₂ in the two-pollutant model, these resultant differences were not significant (Table 3). Given minimal differences in the impacts of air pollution between one-pollutant and two-pollutant models, it was assumed that the influence of each air pollutant on blood biomarkers was predominant (Table S1-5).

Discussion

Thus far, the evidence of air pollution exposure in rural areas on peripheral white blood cells and inflammation biomarkers is scarce and inconsistent. This study revealed significant associations of short-term exposure to ambient air pollution with peripheral white blood cells

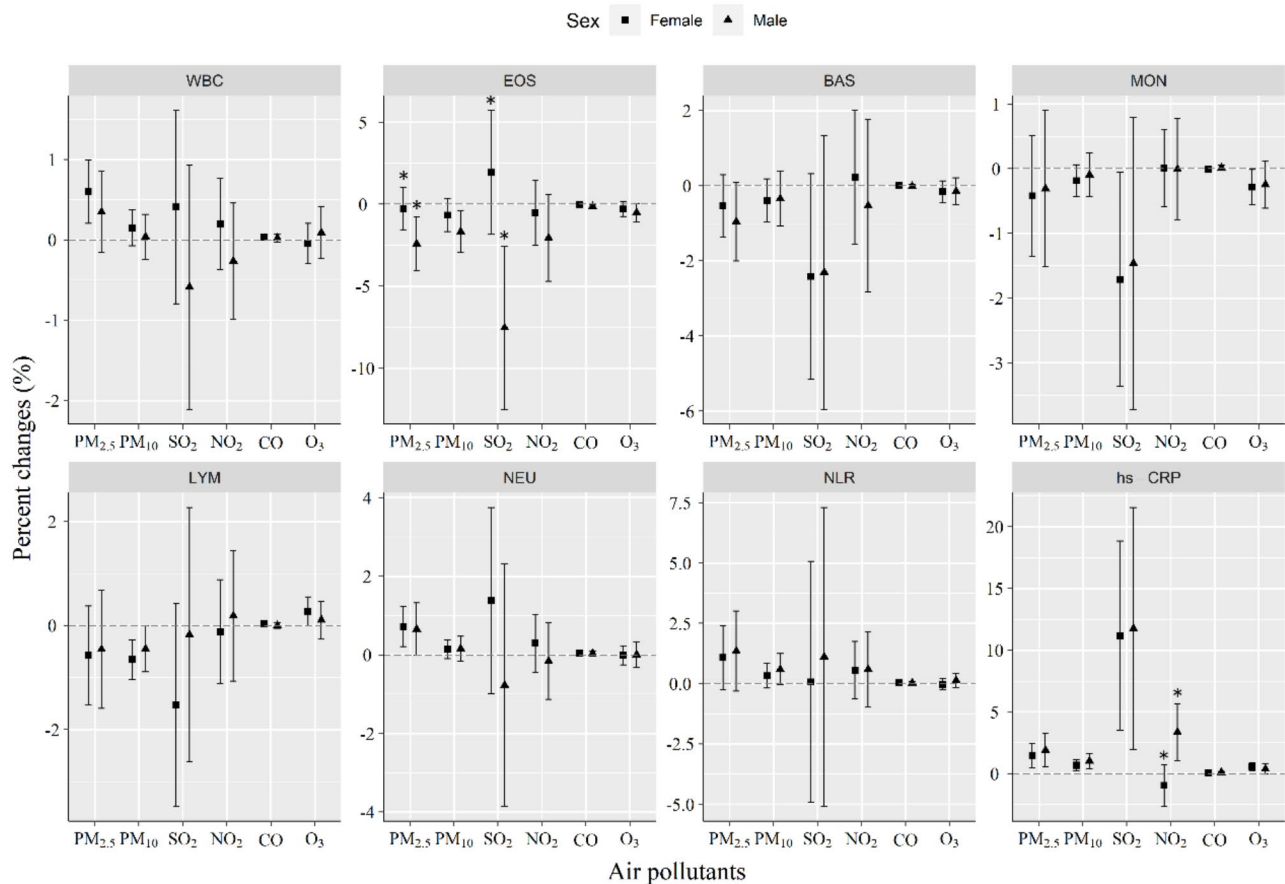


Fig. 3 Changes in age-stratified effects on blood biomarkers associated with a 10 µg/m³ increase in concentrations of air pollutants. The effects were represented as percentage changes (%) for each 10 µg/m³ changes in air pollution concentrations. Older, age ≥ 60 years; Younger, age < 60 years

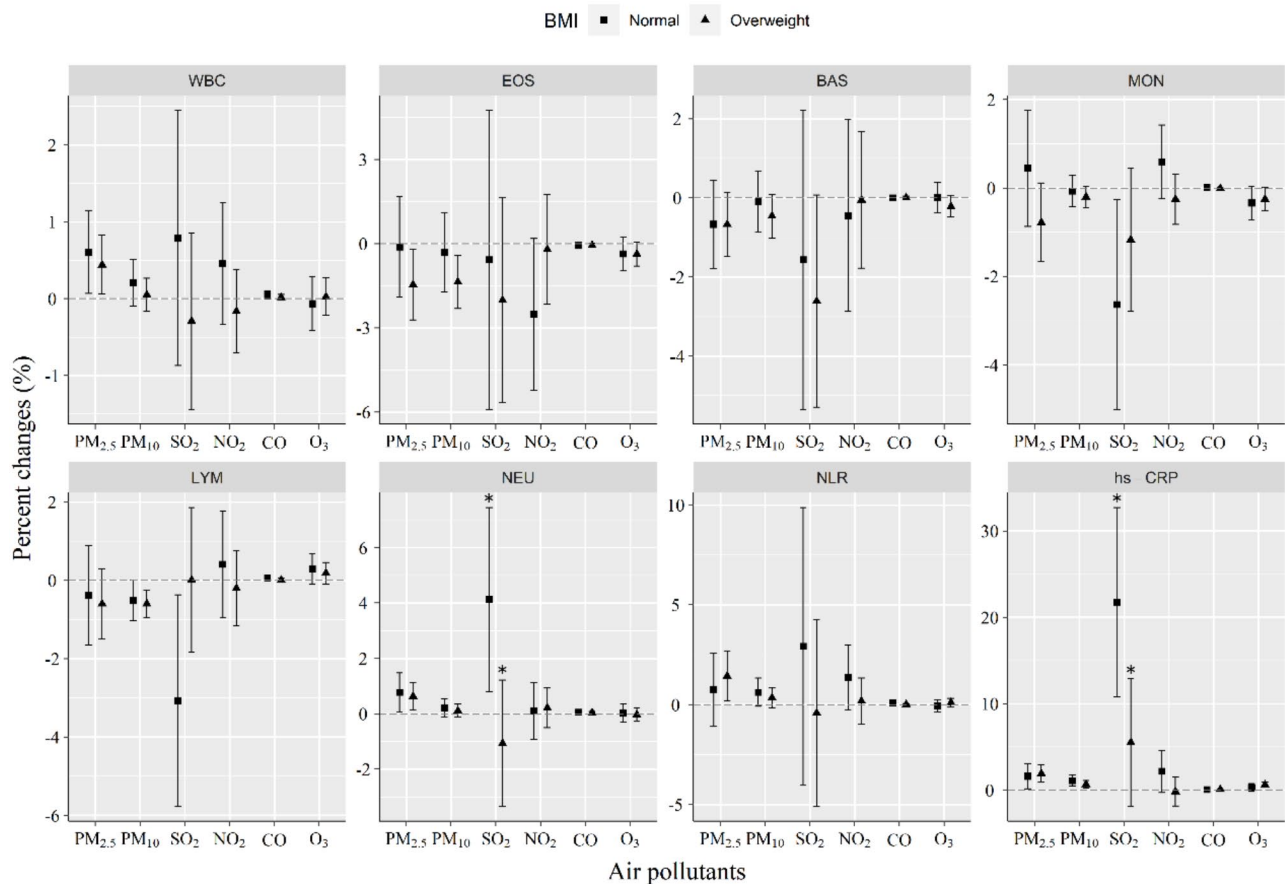


Fig. 4 Changes in sex-stratified effects on blood biomarkers associated with a 10 µg/m³ increase in concentrations of air pollutants. The effects were represented as percentage changes (%) for every 10 µg/m³ changes in air pollution concentrations

and a serum inflammatory biomarker of the population living in rural areas of Northern Henan Province, China. Interestingly, men, normal BMI, current smokers, and old age rendered the participants more susceptible to the harmful effects induced by air pollution exposure.

WBC are considered as systemic effector cells of inflammatory stimuli [25]. In the present study, we found that exposure to PM_{2.5} and CO significantly increased WBC count, while SO₂ exposure markedly reduced WBC count. These findings were consistent with the previous reports. For example, previous studies with an American population and a Chinese community have shown that short-term exposure to ambient PM_{2.5} enhances counts of circulating WBC [26, 27]. Increased WBC count following CO exposure was also reported in a Japanese population [14]. The underlying mechanism for WBC effect is assumed to be due to released cytokines in the circulation, further rendering leukocyte mobilization from bone marrow [28]. An interesting finding from 125 healthy young adults was that exposure to lower levels of gaseous and particulate pollution did not significantly boost WBC counts [29]. Another study showed that circulating WBC count was even reduced following short-term exposure

to atmospheric PM in postmenopausal women aged 50–79 years [30]. Whether these discrepancies in WBC effect were due to the curvilinear association of SO₂ with WBC counts remains unclear [31]. In addition, the variations in the study subjects’ demographics and exposure to air pollution over time may also have an impact.

The present study discovered that the subtypes of WBC including EOS, BAS, and MON were also significantly associated with air pollution exposure. Specifically, exposure to PM_{2.5}, PM₁₀, NO₂, CO, and O₃ were negatively related to EOS counts, while exposure to PM_{2.5}, SO₂, and CO were also negatively related to BAS counts. Moreover, gaseous air pollutants including SO₂, NO₂, and O₃ exposures were negatively associated with MON counts. In addition, this study also showed that short-term exposures to PM_{2.5}, PM₁₀, SO₂, and NO₂ decreased LYM counts but CO and O₃ exposures increased LYM counts. Noteworthy, exposures to PM_{2.5}, PM₁₀, SO₂, and CO were significantly correlated with the increase in NEU counts. These findings were in line with some previous studies. For instance, in a study with 31 subjects from five different locations, Steenhof et al. reported a negative correlation between NO₂ exposure and LYM counts,

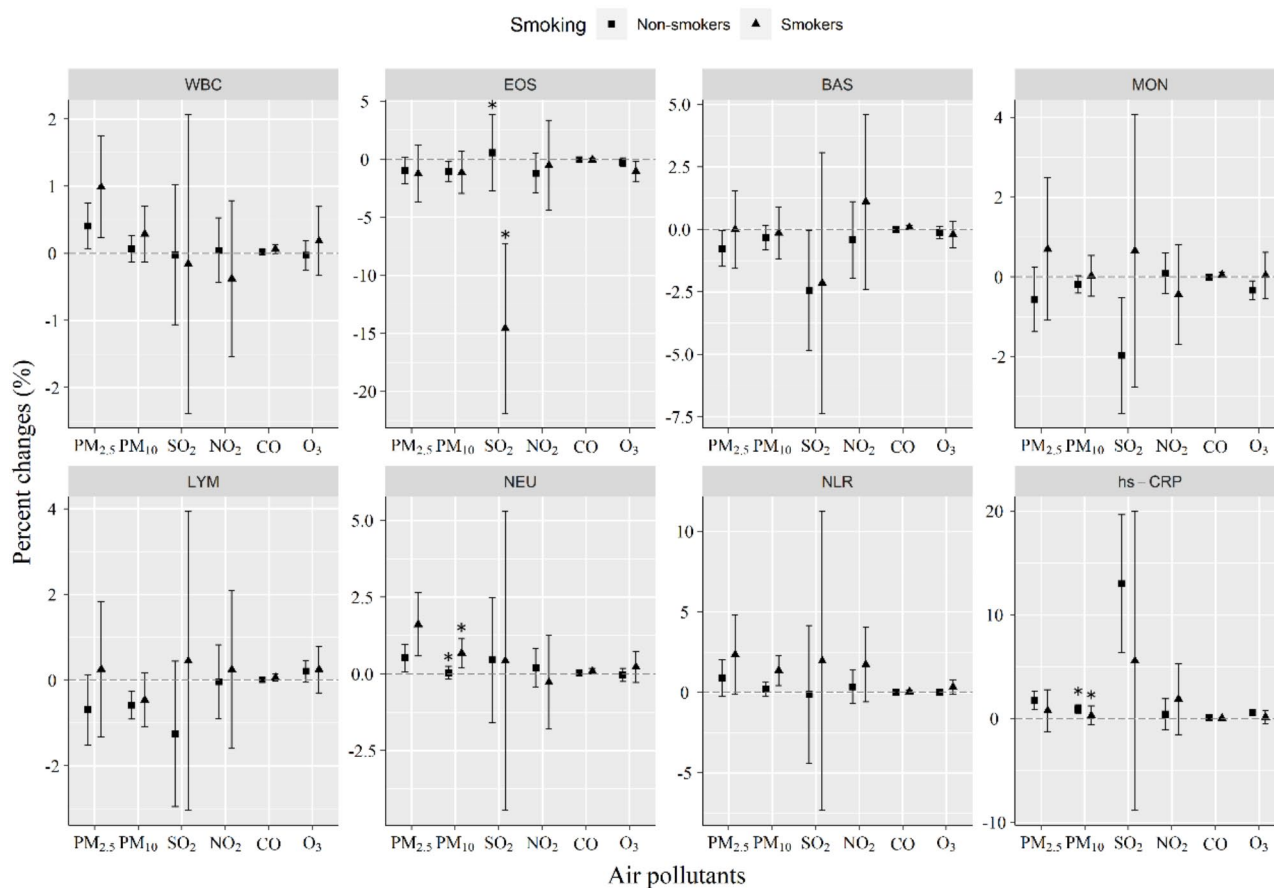


Fig. 5 Changes in BMI-stratified effects on blood biomarkers associated with a 10 µg/m³ increase in concentrations of air pollutants. The effects were represented as percentage changes (%) for every 10 µg/m³ changes in air pollution concentrations. Normal, BMI < 24 kg/m²; Overweight, BMI ≥ 24 kg/m²

and a positive association of PM with NEU counts [15]. In another study of healthy men in North Carolina, USA, Riediker et al. showed that exposure to PM_{2.5} was negatively correlated with LYM and positively associated with NEU count [32]. Additionally, a Copenhagen research showed that short-term exposure to ambient CO increased counts of NEU and LYM [14]. However, there was one study showing no correlation between exposure to air pollution and BAS, EOS, and MOS counts of healthy people’s [33]. Another study with non-smoking, healthy adults living in northern France demonstrated that exposure to lower concentrations of O₃ was associated with a significantly higher EOS count [34]. In addition, an investigation of 15 healthy volunteers showed a decrease in LYM after short-term exposure to O₃ [35]. A recent study with an urban population reported a significant positive association between NEU and LYM counts and short-term exposure to air pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, CO, O₃) [13]. Overall, the associations of ambient air pollution with the subtypes of WBC counts appeared to be air pollutant- and cell type-dependent, and were also affected by the participant’s health status,

air pollution levels, and the physicochemical characteristics of air pollutants.

NLR has been proposed as a more sensitive and systemic biomarker of inflammation and immune responses induced by diverse stimuli [36–39]. However, the studies used NLR as a biomarker of air pollutant effects on humans are limited and inconsistent. For instance, a Swedish epidemiological investigation revealed that moderate PM_{2.5} and PM₁₀ exposures were associated with increased NLR [40]. In contrast, a study of Chinese schoolchildren did not find significant alteration in NLR between the polluted and control areas [41]. Interestingly, according to a cross-sectional study of urban Chinese adults, exposure to CO was positively correlated with NLR whereas exposure to PM₁₀ negatively correlated with NLR [13]. This present study in rural areas showed an association between short-term exposures to PM_{2.5}, PM₁₀, SO₂, and CO with elevations in NLR, suggesting that exposure to air pollutants induced systemic immunological and inflammatory responses.

Hs-CRP is the specific biomarker of low but persistent levels of inflammation [20]. A previous study has demonstrated that short-term exposure to either PM_{2.5} or

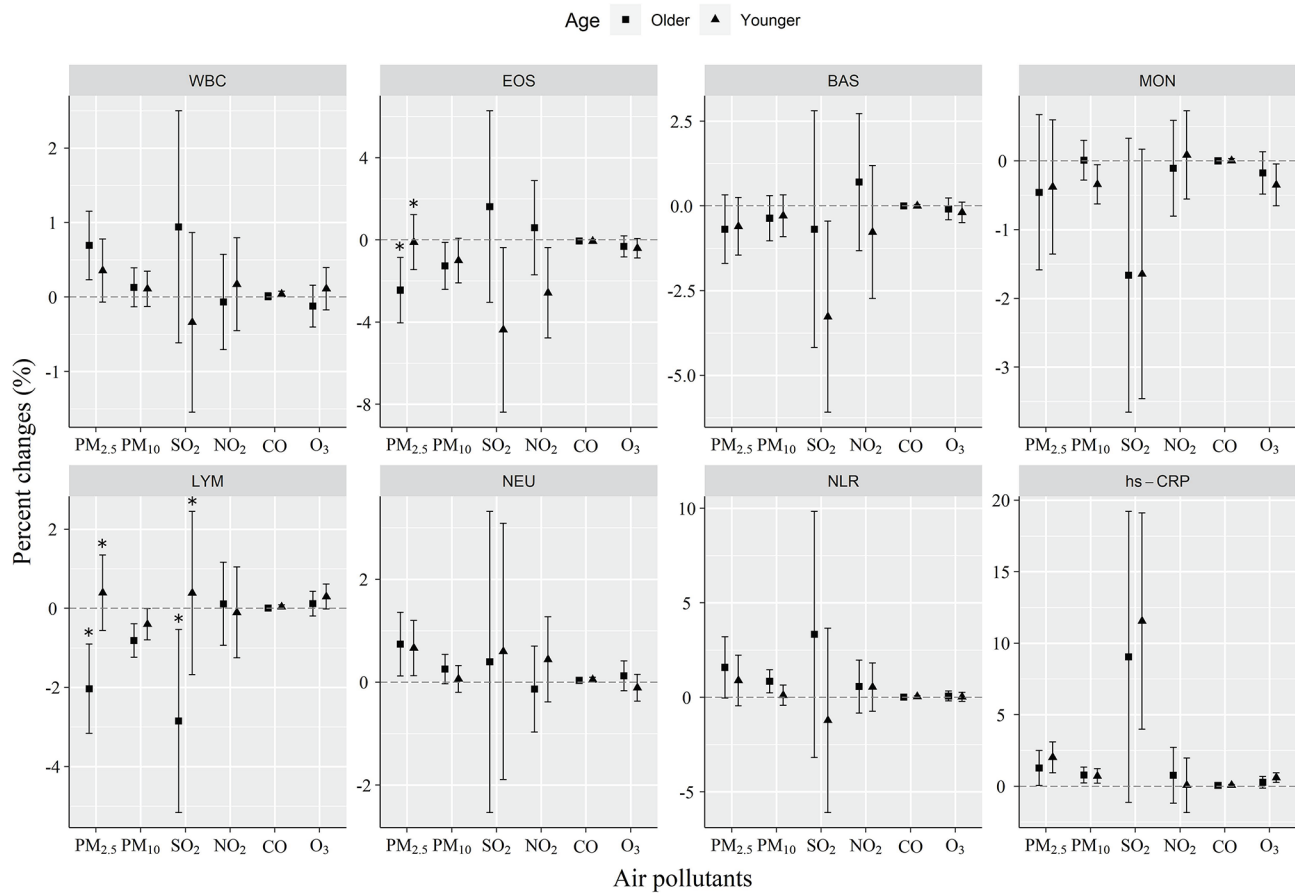


Fig. 6 Changes in smoking-stratified effects on blood biomarkers associated with a 10 µg/m³ increase in concentrations of air pollutants. The effects were represented as percentage changes (%) for every 10 µg/m³ changes in air pollution concentrations. Non-smokers, never or former smokers; Smokers, current smokers

Table 3 Percent Changes (95% CI) of immunological and inflammatory biomarkers with a 10 µg/m³ increase in PM_{2.5} in two-pollutant model

	WBC (%)	EOS (%)	BAS (%)	MON (%)	LYM (%)	NEU (%)	hs-CRP (%)	NLR (%)
PM _{2.5}	0.51 (0.19, 0.82)	-1.06 (-2.09, -0.04)	-0.65 (-1.3, 0)	-0.35 (-1.09, 0.38)	-0.53 (-1.26, 0.2)	0.7 (0.29, 1.1)	1.62 (0.82, 2.43)	1.19 (0.16, 2.22)
PM _{2.5} +PM ₁₀	0.54 (0.22, 0.99)	-1.05 (-2.08, 1.48)	-0.64 (-1.3, -0.03)	-0.38 (-1.12, -0.28)	-0.49 (-1.27, 0.53)	0.75 (0.32, 2.43)	1.95 (1.11, 17.96)	1.17 (0.12, 4.46)
PM _{2.5} +SO ₂	0.51 (0.19, 0.46)	-1.02 (-2.08, 0.53)	-0.64 (-1.33, 1.29)	-0.35 (-1.08, 0.49)	-0.65 (-1.41, 0.78)	0.7 (0.29, 0.72)	1.62 (0.79, 1.92)	1.17 (0.13, 1.52)
PM _{2.5} +NO ₂	0.51 (0.2, 0.06)	-1.11 (-2.13, 0)	-0.65 (-1.3, 0.03)	-0.4 (-1.18, 0.02)	-0.55 (-1.3, 0.06)	0.7 (0.3, 0.08)	1.68 (0.87, 0.1)	1.4 (0.3, 0.06)
PM _{2.5} +CO	0.48 (0.16, 0.2)	-1.08 (-2.1, -0.04)	-0.72 (-1.39, 0.08)	-0.49 (-1.24, -0.06)	-0.75 (-1.49, 0.44)	0.7 (0.28, 0.19)	1.53 (0.72, 0.74)	1.44 (0.37, 0.22)
PM _{2.5} +O ₃	0.49 (0.18, 0.82)	-1.06 (-2.08, -0.05)	-0.75 (-1.41, -0.07)	-0.28 (-1.02, 0.39)	-0.43 (-1.17, -0.16)	0.69 (0.28, 1.15)	1.57 (0.76, 2.36)	1.18 (0.15, 2.37)

The statistically significant estimates are highlighted in bold. WBC: white blood cells; EOS: eosinophils; BAS: basophils; MON: monocytes; LYM: lymphocytes; NEU: neutrophils; hs-CRP: high-sensitivity C-reactive protein

PM₁₀ raised hs-CRP levels, with PM_{2.5} having a larger effect than PM₁₀ [42]. In addition, gaseous air pollutants including SO₂, NO₂, and CO also induced significant increases in hs-CRP [19]. In line with these observations, this study revealed positive correlations between PM_{2.5},

PM₁₀, SO₂, NO₂, CO, or O₃ and hs-CRP, and PM_{2.5} also showed a stronger effect than PM₁₀. Whether air pollution-induced oxidative stress is involved in this process remains to be elucidated [43, 44].

This study revealed that men, individuals with normal BMI, current smokers, and those older than 60 years were also shown to be more vulnerable to the harmful effects of acute exposure to air pollutants. The impact of sex factor may be due to biological and lifestyle differences between males and females, the latter having better innate immunity than men [45, 46]. The effects of SO₂ exposure on NEU and hs-CRP were more evident in the non-overweight population than in the overweight population in this study. Similarly, a previous research demonstrated that the effect of PM₁₀ on hs-CRP was more evident in non-obese individuals [47]. The explanation for this observation could be that the people with obesity or overweight had slightly higher baseline of oxidative stress and inflammation, rendering the effects of air pollution in these people difficult to identify [48]. Both air pollutants and cigarettes have been reported to induce acute epithelial injury and neutrophil inflammation [49, 50]. It is assumed that the airways of smokers are vulnerable to air pollutant adverse effects [51–53]. With regard to the age, the elderly are more susceptible to health problems when exposed to air pollutants given their age-related impairment of immune system, ineffective cardiovascular and respiratory systems, and existence of other adverse co-factors [54].

The present study was conducted on a rural population to assess the effects of short-term exposure to air pollution on peripheral white blood cells and serum inflammatory biomarker. A study conducted on a population in Kaohsiung City, Japan, showed similar results, with air pollution exposure being associated with white blood cells alterations, implying that air pollution is associated with systemic inflammation in humans [14]. Another study conducted on 22 healthy young subjects from highly polluted urban areas and low-polluted rural areas, respectively, demonstrated that air pollution was associated with hs-CRP and white blood cells levels, with a greater effect on leukocyte counts in urban populations probably due to differences in air pollution levels, sources and other socioeconomic factors between urban and rural areas [55].

This study used peripheral leukocytes and a serum inflammatory biomarker as exposure outcomes to assess the potential response to short-term air pollution exposure on populations in rural areas, with the innovative use of NLR as a composite marker. The strength of this study mainly lied on the use of comprehensive data of sociodemographic characteristics, lifestyle, health conditions, and other factors. In addition, all results were adjusted for potential confounders, which made the findings of the study more robust and credible. Several limitations should also be pointed out for this study. First, air pollution exposure might be underestimated using monitoring station data since environmental monitoring

stations might not accurately capture personal exposure levels, especially if individuals spend significant time indoors or away from the monitoring locations. In addition, air pollutant levels could vary significantly over small distances and short time periods, which might not be captured fully by the data from monitoring stations. Second, there could be additional uncontrolled confounding factors in the study, such as indoor air pollution or occupational exposures, or socioeconomic status, which might influence both exposure and biomarker levels. Third, some biomarkers used in this study might not be sensitive enough to detect subtle changes caused by short-term exposures, or they may not reflect longer-term health effects.

Conclusions

This cross-sectional study on a rural population revealed that short-term exposure to ambient air pollutants was associated with alterations of blood inflammatory biomarker, offering new epidemiological evidence for understanding air pollution adverse effects on the health of rural residents. Examination of blood samples for inflammatory biomarkers is important in these rural populations because it not only helps individuals and communities understand their health status, but also helps the early detection of many common diseases, such as diabetes and hypertension. This may reduce healthcare costs and improve the overall health of the rural population. Future researches will investigate long-term exposure to air pollution on peripheral white blood cells and inflammation biomarkers to test the validity of these cellular and molecular biomarkers in rural populations. Animal models will also be introduced to examine the causal relationship between exposure to ambient air pollutants collected from rural areas and systemic inflammation, and examine intervention measures.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12889-024-19116-2>.

Supplementary Material 1

Acknowledgements

The field investigator and all participants are acknowledged by the authors for their contributions to this study.

Author contributions

Yishu Yang: Investigation, Methodology, Data collection, Verification, Visualization, Software, Formal analysis, writing – original draft. Hui Wu: Methodology, Software, Validation, Visualization, Writing-review. Fei Xu: Investigation, Methodology, Validation. Shuaiqi Zhao: Methodology, Validation. Yuling Zeng: Methodology, Validation. Ling Zhang: Methodology, Validation. Zhen An: Investigation, Methodology, Validation. Huijun Li: Investigation, Methodology, Validation. Juan Li: Investigation, Methodology, Validation. Jie Song: Methodology, Software, Validation, Visualization. Weidong Wu: Conceptualization, Funding acquisition, Supervision, Writing-review & editing,

Project administration, Resources, Validation. All authors read and approved the final manuscript.

Funding

This work was supported by the National Key Research and Development Program Precision Medicine Initiative of China (2016YFC0900803), and the National Natural Science Foundation of China (81961128031; 81573112).

Data availability

The data used and/or analyzed during the study will be available upon the request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Xinxiang Medical University for Human Studies authorized this investigation (XYLL-2016242). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that influence the work reported in this paper.

Received: 7 April 2024 / Accepted: 12 June 2024

Published online: 26 June 2024

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