Short-term exposure to fine particulate matter and its constituents may affect renal function via oxidative stress: A longitudinal panel study

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HIGHLIGHTS

- Short-term exposure to PM\textsubscript{2.5} may affect renal function among healthy adults.
- Ad, Pb, As, Se, Tl and IPY in PM\textsubscript{2.5} might contribute to the association.
- Oxidative stress might be a bio-pathway between PM\textsubscript{2.5} and renal function.

GRAPHICAL ABSTRACT

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ABSTRACT

Exposure to fine particulate matter (PM\textsubscript{2.5}) has been reported to increase the risks of chronic kidney disease. However, limited research has assessed the effect of PM\textsubscript{2.5} and its constituents on renal function, and the underlying mechanism has not been well characterized. We aimed to evaluate the association of PM\textsubscript{2.5} and its constituents with kidney indicators and to explore the roles of systematic oxidative stress and inflammation in the association. We conducted a longitudinal panel study among 35 healthy adults before-, intra- and after-the 2019 Wuhan Military World Games. We repeatedly measured 6 renal function parameters and 5 circulating biomarkers of oxidative stress and inflammation at 6 rounds of follow-ups. We monitored hourly personal PM\textsubscript{2.5} concentrations with 3 consecutive days and measured 10 metals (metalloids) and 16 polycyclic aromatic hydrocarbons (PAHs) components. The linear mixed-effect models were applied to examine the association between PM\textsubscript{2.5} and renal function parameters, and the mediation analysis was performed to explore potential bio-pathways. PM\textsubscript{2.5} concentrations across Wuhan showed a slight decrease during the Military Games. We observed significant associations between elevated blood urea nitrogen (BUN) levels and PM\textsubscript{2.5} and its several metals and PAHs components. For an interquartile range (IQR) increase of PM\textsubscript{2.5}, BUN increased 0.42 mmol/L (95% CI: 0.14 to 0.69). On average, an IQR higher of lead (Pb), cadmium (Cd), arsenic (As), selenium (Se), thallium (Tl) and Indeno (1,2,3-cd) pyrene (IPY) were associated with 0.90, 0.65, 0.29, 0.27, 0.26 and 0.90 mmol/L increment of

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1. Introduction

Renal dysfunction has gradually become a global public concern because of the increasing burden of chronic kidney disease (CKD) (Eknoyan et al., 2004; Couser et al., 2011). A study among 12 countries reported that the prevalence of CKD was 14.3% (Ene-Iordache et al., 2016), and it was estimated that 119.5 million CKD patients diagnosed in China (Zhang et al., 2012). Thus, it is urgent to identify the risk factors for reducing disease burden. Recent studies indicated that environment pollution, especially air pollution, may serve as an important risk factor of CKD (Xu et al., 2018; Al-Aly and Bowe, 2020; Stenvinkel et al., 2020).

A modeling study estimated that 6.59 million disability-adjusted life years of CKD (Xu et al., 2018; Al-Aly and Bowe, 2020; Stenvinkel et al., 2020). Reported that the prevalence of CKD was 14.3% (Ene-Iordache et al., 2016), because of the increasing burden of chronic kidney disease (CKD) (Eknoyan et al., 2004; Couser et al., 2011). A study among 12 countries among 2.5 million young adults reported that each 10 μg/m³ increment of PM2.5 pollution (Bowe et al., 2020). It is of great public health significance to explore the adverse effects of PM2.5 on kidney and elucidate potential pathogenic mechanisms.

As a metabolic organ that maintains the fluid and acid-base balance, the filtration and concentration function of kidney make it vulnerable to environmental pollutants (Xu et al., 2018). Several pivotal blood renal function parameters were reported to be significantly associated with PM2.5 (Rahmani Sani et al., 2020; Wu et al., 2020; Zhao et al., 2020; Kuźma et al., 2021; Li et al., 2021). For example, a cross-sectional study among 2.5 million young adults reported that each 10 μg/m³ increment of PM2.5 in 3-years average exposure was associated with 0.85% decrease of eGFR (Li et al., 2021). Another research on rodent models found that sub-chronic exposure to PM2.5 could lead to elevated blood urea nitrogen (BUN) levels (Tavera Busso et al., 2018). However, most previous research focused on pregnant women (Zhao et al., 2020), children (Liu et al., 2020) or the elderly (Mehta et al., 2016; Fang et al., 2020), while the associations among healthy adults was not fully characterized. Additionally, PM2.5 is a heterogeneous mixture with nephrotoxic constituents, which may contribute to the major association between PM2.5 and renal dysfunction. Some studies reported that metals and polycyclic aromatic hydrocarbons (PAHs) in PM2.5 were related to oxidative damages and heart rate variability (Wei et al., 2009; Wu et al., 2011). However, limited evidence is available for the association between PM2.5-bound components and renal function.

The underlying bio-pathways for the association between PM2.5 and renal function remain uncertain. Previous reviews reported that exposure to PM2.5 may increase oxidative stress (Li et al., 2020) and inflammation (Tang et al., 2020), and these responses were found to be related with renal dysfunction in some populations (Yilmaz et al., 2006; Upadhay et al., 2011; Correia-Costa et al., 2016). Since kidney is a highly vascularized organ and is susceptible to vascular dysfunction (Lue et al., 2013). Increased states of vasoconstriction and blood coagulation may decrease renal blood flow, further weakening the filtration function of the kidney. An experimental study in the rodent model reported that chronic exposure to PM2.5 could trigger inflammation and oxidative stress pathways which contributed to the PM2.5 induced kidney injury (Chenu et al., 2018). Another research in rat model reported that PM2.5 may induce early kidney damage by activating systematic inflammation and oxidative stress response (Aztatzi-Aguilar et al., 2016). However, evidence about the underlying mechanisms remain scarce.

Therefore, we designed the current research with personal PM2.5 exposure and components measurements to explore their acute adverse effects on renal function parameters among healthy adults. In addition, we explored the possible mediation effect of circulating biomarkers on the aforementioned associations. The results of our research will contribute to the evidence of the association between PM2.5 and renal function and serve the potential bio-pathway.

2. Material and methods

2.1. Study design and participants

The 7th Military World Games were held in Wuhan, China, from October 18 to October 27, 2019. A series of policy measures were implemented to restrict the road traffic and control air pollution during the match. In our previous research (Peng et al., 2022), we recruited 70 college students for 8 rounds repeated measurements of blood samples collection, in-person investigation and physical examination to explore the adverse effects of PM2.5. Baseline demographic information, including sex, date of birth, weight, height, education was collected after signing the informed consent. We randomly selected a subset from the previous research for the current research. Briefly, 35 healthy adults were included with 6 rounds follow-up visits including twice in each of the three phases before (from Sep. 16th to Sep. 27th), during (from Oct. 17th to Oct. 28th) and after the Military games (from Dec. 5th to Dec. 16th). We measured individual-level hourly PM2.5 concentrations, and collected the venous blood at the 4th day. And participants were required to reported health status (Healthy or Sick), medication use (Yes or No), caffeine and alcohol consumption (Yes or No), exercise (Yes or No) and dietary intake frequency at each follow-up visit. The research design was approved by Wuhan University Medical Ethics Committee.

2.2. Exposure measurement

We conducted the personal hourly PM2.5 measurements for 3-consecutive day before each physical examination. We performed the HUAWEI individual PM2.5 monitor which was designed with low weight for portability based on Beta ray attenuation methods. And the DUST-TRAK™ DRX 8534 (TSI, USA) was used to calibrate personal exposure devices (Peng et al., 2022). Ambient PM2.5 samples were collected by a medium-volume sampler (TH-150C, Wuhan Tianhong Environment Protection Industry Co. Ltd., Wuhan, China) with Whattman quartz fiber filters (Whatman International Ltd., Maidstone, UK) and kept individually in a polystyrene box (SF-90BOX, Beijing Safelab Ltd, Beijing, China). The constituents of ambient PM2.5, including trace metals (metaloids) and the polycyclic aromatic hydrocarbons (PAHs) measured by Inductively Coupled Plasma-Mass Spectrum with iCAP-Q (Thermo Fisher Scientific, Waltham, MA, USA) and Gas Chromatography-Mass Spectrometry with Trace 1300-ISQ 7000 (Thermo Fisher Scientific, Waltham, MA, USA), respectively. All experimental manipulations were done at the laboratory of Wuhan Center for Disease Control and Prevention and details can be found in the previous research (Mao et al., 2020). Generally, 10 metals and 16 PAHs were measured from PM2.5, such as Aluminum (Al), Arsenic (As), Cadmium (Cd), Lead (Pb), Selenium (Se), Thallium (Tl), Indeno (1,2,3-cd) pyrene (IPY), etc. Additionally, we collected the city-level PM2.5 concentrations from 2018 to 2020 from Wuhan Municipal Ecological Environment Bureau (http://hbj.wuhan.gov.cn/) to evaluate the effect of restrictive measures during the Military World Games. The hourly concentrations of ozone (O3), nitrogen dioxide (NO2), sulfate dioxide (SO2) and carbon monoxide (CO) was also collected from the nearest air monitoring station (Wuhan Donghu Liyuan).

2.3. Blood collection and analysis

Fasting venous blood samples (20 mL in total, including 10 mL EDTA
anticoagulated blood and 10 mL non-anticoagulated blood) were collected before 8:00 a.m. at each physical examination. And the centrifuged plasma and serum samples were stored at −80 °C before biomarkers measurement. Renal function indicators including BUN, sCr, and urea acid (UA) were detected by a full-automatic biochemical analyzer (Hitachi 7600, Hitachi Co., Tokyo, Japan). The blood urea nitrogen-to-creatinine ratio (BUN/sCr) was calculated as a commonly clinical renal function indicator. The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration Equation (Levey et al., 2009), and the values of endogenous creatinine clearance rate (Ccr) were estimated following the Cockcroft-Gault Equation (Cockcroft and Gault, 1976; Winter et al., 2012). The fasting blood glucose concentrations were measured by an automatic biochemical analyzer (Cobas c701, Roche, Japan). The following 5 circulating biomarkers were measured as potential bio-mediators: (i) inflammation: Hypersensitive C-reactive protein (hsCRP), interleukin-6 (IL-6); (ii) coagulation: fibrinogen (FIB); (iii) oxidative stress: superoxide dismutase (SOD); (iv) vasoconstriction: Angiotensin-converting enzyme (ACE). The serum hsCRP and ACE were analyzed through the Beckman Coulter AUS8000 (Beckman Coulter Inc., Brea CA, USA). SOD was analyzed using an automatic biochemical analyzer (Hitachi 7180, Hitachi, Tokyo, Japan) with Superoxide Dismutase Kit. The serum IL-6 was assayed by electrochemiluminescence on Roche cobas 8000 (Roche Diagnostics, Mannheim, Germany). The plasma FIB was analyzed by the Claus method on SF-8200 coagulation analyzer (Beijing Succeeder Technology Inc., Beijing, China). All the biomarkers were analyzed in the laboratory of Wuhan Pulmonary Hospital (Wuhan, China).

2.4. Statistic analysis

Demographics, biological indicators and PM2.5 concentrations were described as mean ± standard deviation (SD) or frequency (%). The linear mixed-effect (LME) model with each participant as random intercept was performed to assess the relationship between PM2.5 exposure and renal function. We calculated the 1–3 days PM2.5 moving average (ave 0–1, ave 0–2 and ave 0–3) to identify the cumulative impact of exposure in the single-pollutant LME model. A group of prior covariates were adjusted in the LME model, including age, sex, body mass index, exercise, caffeine consumption, alcohol consumption, fasting blood glucose. Additionally, the temperature and relative humidity were adjusted in the form of natural splines, while the Aikaie information criterion was applied to determine the degrees of freedom. Besides, as previous review reported that high-protein diets serve as a risk factor for renal dysfunction (Ko et al., 2020), we adjusted the high protein proportion food intake (i.e., the consumption frequency of meat, poultry, fish, and milk) in the association between PM2.5 and renal function. We also investigated the short-term association between 3-days moving average of PM2.5 components and renal function indicators in the single-constituent LME model. The effects were estimated as the changes of indicators and 95% confidence intervals (CIs) with an interquartile range (IQR) increment in PM2.5 or its constituents’ concentrations.

We hypothesized that associations of PM2.5 with renal function indicators might be mediated through inflammation, oxidative stress, or vasoconstriction. Therefore, we selected SOD, hsCRP, IL-6, FIB and ACE as potential mediators which were suggested to be associated with PM2.5 in the previous research. In this study, potential mediators were defined by the following criteria: (i) significantly associated with PM2.5 and (ii) significantly associated with renal function indicators (Valeri and Vanderweele, 2013). Two LME models were built for the mediation analysis (Bind et al., 2016), one fitting for the PM2.5–mediator association and the other one fitting for the mediator-renal function association (Equations (1) and (2)).

$$M_{ij} = \beta_0 + u_i + \beta_{PM2.5} s_{PM2.5ij} + \beta_{Xij} x_{ij} + \ldots + \beta_{p} x_{pj} + e_{ij} \quad [1]$$

$$Y_{ij} = \gamma_0 + g_i + \gamma_{PM2.5} s_{PM2.5ij} + \gamma_{Xij} x_{ij} + \ldots + \gamma_{p} x_{pj} + \eta_{ij} \quad [2]$$

In both of two equations, $\gamma_0$ and $\eta_0$ correspond to the intercept for the population mean; $u_i$ and $g_i$ correspond to the subject-specific random intercept. $M_{ij}$ correspond to the potential circulating biomarkers and $Y_{ij}$ correspond to the renal function indicators measured for an individual $i$ ($i = 1, ..., 35$) at visit $j$ ($j = 1, ..., 6$). $X_{ij}$ to $x_{pj}$ represent the priori-selected covariates, and $\eta$ and $\eta_j$ represent the within-subject error term. $\gamma_{PM2.5}$ represents the natural direct effect (NDE), and the natural indirect effect (NIE) could be given by $\beta_{PM2.5} \times \gamma_{PM2.5}$. The proportion mediated, which means the percentage of NIE over the total effect, was calculated by (NIE/NIE + NDE).

To examine the robustness of our findings, we performed several sensitivity analyses. Firstly, outcomes of the previous visit might be potential confounding factors for subsequent visits and lead to bias in the longitudinal studies. Therefore, we built a LME model regression between $Y_{ij}$ (BUN/i) and $M_{ij}$ (SOD/i) to examine the time-varying confounding assumption (Fig. S1). Then, we adjusted the other four gaseous pollutants (i.e., O₃, SO₂, NO₂ and CO) into the two-pollutant models. Thirdly, we fitted a “constituent-PM2.5 joint model” and “constituent-residual model” to eliminate the extraneous variation of total PM2.5 and the collinearity between constituent and the PM2.5 mass concentrations (Liu et al., 2017). All the statistical analyses were conducted in the R software (4.0.5) with packages of “lmerTest”, “splines” and “mediation”, and the two-side p-value less than 0.05 was determined as statistical significance.

3. Results

3.1. Descriptive analysis

A total of 35 volunteers (28 females and 7 males) with an averaged age of 20.43 years and a mean BMI of 21.17 kg/m² were recruited in this panel study. And all the participants were nonsmokers. However, 4 participants failed to complete 1 follow-up visit and 1 participant failed to complete 2 follow-up visits for various reasons and thus 6 observations were deleted. Eventually we examined a total number of 204 venous blood samples. Table 1 showed the 12 blood biomarkers levels, including the 6 renal function indicators (BUN, sCr, UA, eGFR, Ccr, BUN/sCr), the 5-potential bio-mediators (SOD, IL-6, hsCRP, ACE, FIB).

Table 1

| Demographic characteristics | Mean ± SD or N (%) |
|-----------------------------|-------------------|
| NO.                         | 35                |
| Age, years                  | 20.43 ± 1.74      |
| BMI, kg/m²                  | 21.17 ± 2.59      |
| Sex, female                 | 28 (80.00%)       |

| Serum and plasma biomarkers | Mean ± SD or N (%) |
|-----------------------------|-------------------|
| FBG, mmol/L                 | 4.61 ± 0.37       |
| SOD, U/ml                   | 146.79 ± 9.43     |
| FIB, g/L                    | 2.44 ± 0.41       |
| hsCRP, mg/dL                | 0.99 ± 0.13       |
| IL-6, pg/mL                 | 1.87 ± 1.75       |
| ACE, U/L                    | 33.00 ± 10.00     |

| Renal function indicators  | Mean ± SD or N (%) |
|-----------------------------|-------------------|
| BUN, mmol/L                 | 3.86 ± 1.21       |
| eGFR, ml/(min*1.73m²)       | 123.79 ± 10.12    |
| Ccr, ml/(min*1.73m²)        | 118.63 ± 20.61    |
| BUN/sCr                     | 15.52 ± 4.74      |

Abbreviations: SD, standard deviation; BMI, body mass index; FBG, fasting blood glucose; SOD, superoxide dismutase; FIB, fibrinogen; hsCRP, hypersensitive C-reactive protein; ACE, angiotensin converting enzyme; IL-6, interleukin-6; BUN, blood urea nitrogen; sCr, serum creatinine; UA, blood urea acid; eGFR, estimated glomerular filtration rate; Ccr, endogenous creatinine clearance; BUN/sCr, the ratio of blood urea nitrogen to serum creatinine.
and the fasting blood glucose. Fig. S2 showed the monthly averaged PM$_{2.5}$ concentrations in Wuhan from September to December for the years of 2018–2020. We found an upward trend of ambient PM$_{2.5}$ concentrations during the 4 months in 2018 and 2020, while the concentrations showed a slight decline in October (during the 7th Military World Games) in 2019. Table 2 summarized PM$_{2.5}$ mass concentrations along with metals and PAHs constituents during the whole research periods. The average individual PM$_{2.5}$ concentrations were 42.54 μg/m$^3$, which exceed the Interim Target-2 standard of the WHO air quality guideline on PM$_{2.5}$. Among the various constituents of the PM$_{2.5}$, the metal/metalloid constituents had the higher proportion than PAHs and varied considerably, in which Al, Pb and Mn had large abundant while Ni, Cd and Tl were less.

3.2. Estimated association between PM$_{2.5}$ and renal function

Fig. 1 presented the estimated associations of PM$_{2.5}$ concentrations with renal function indicators (BUN, sCr, UA, eGFR, Ccr and BUN/sCr). Short-term exposure to PM$_{2.5}$ were positively associated with BUN and BUN/sCr. An IQR increase in PM$_{2.5}$ (32.94 μg/m$^3$) was associated with 0.30 mmol/L (ave 0–2, 95% CI: 0.05 to 0.55) and 0.42 mmol/L (ave 0–3, 95% CI: 0.14 to 0.69) increment of BUN, respectively. For the BUN/sCr, an IQR increment in PM$_{2.5}$ was associated with 1.29 (ave 0–2, 95% CI: 0.27 to 2.30) and 1.74 (ave 0–3, 95% CI: 0.58 to 2.86) elevated in BUN/sCr, respectively. However, the estimated effect of PM$_{2.5}$ on other renal function indicators were not significant.

Table 2

| Metals (ng/m$^3$) | 25th | 50th | 75th | IQR     |
|------------------|------|------|------|---------|
| Sb               | 2.60 | 1.24 | 1.77 | 2.72    |
| Al               | 148.77 | 61.89 | 114.12 | 31.46 |
| As               | 6.09 | 3.54 | 4.45 | 5.24    |
| Cd               | 1.30 | 0.66 | 0.87 | 1.20    |
| Cr               | 4.43 | 2.74 | 3.25 | 3.37    |
| Pb               | 65.97 | 32.55 | 45.93 | 36.38 |
| Mn               | 19.35 | 5.49 | 17.46 | 15.85 |
| Ni               | 6.22 | 0.95 | 1.62 | 2.11    |
| Ti               | 0.51 | 0.25 | 0.35 | 0.50    |
| PAHs (ng/m$^3$)  |      |      |      |         |
| NAP              | 0.15 | 0.06 | 0.10 | 0.13    |
| ANO              | 0.37 | 0.09 | 0.37 | 0.40    |
| ANA              | 0.29 | 0.08 | 0.29 | 0.30    |
| FLU              | 0.56 | 0.20 | 0.50 | 0.58    |
| PHE              | 0.47 | 0.12 | 0.45 | 0.49    |
| ANT              | 0.82 | 0.22 | 0.76 | 0.86    |
| FLT              | 0.93 | 0.29 | 0.75 | 0.93    |
| P3R              | 1.05 | 0.31 | 0.99 | 1.06    |
| CHR              | 0.31 | 0.22 | 0.21 | 0.35    |
| BaA              | 0.54 | 0.18 | 0.47 | 0.53    |
| BSF              | 1.32 | 0.34 | 1.23 | 1.39    |
| BKF              | 1.25 | 0.35 | 1.02 | 1.11    |
| BaP              | 1.17 | 0.33 | 1.05 | 1.26    |
| DBA              | 0.54 | 0.13 | 0.43 | 0.54    |
| BPE              | 0.85 | 0.60 | 0.48 | 0.62    |
| IPY              | 0.25 | 0.20 | 0.11 | 0.17    |

Abbreviations: SD, standard deviation; IQR, interquartile range; Sb, Stibium; Al, Aluminum; As, Arsenic; Cd, Cadmium; Cr, Chromium; Pb, Lead; Mn, Manganese; Ni, Nickel; Se, Selenium; Ti, Thallium; PAHs, Polycyclic aromatic hydrocarbons; NAP, Naphthalene; ANA, Acenaphthene; ANY, Acenaphthylene; FLU, Fluorene; PHE, Phenanthrene; ANT, Anthracene; FLT, Fluoranthene; P3R, Pyrene; CHR, Chrysene; BaA, Benzo (a) pyrene; BSF, Benzo (b) fluoranthene; BKF, Benzo (k) fluoranthene; BaP, Benzo (a) pyrene; BPE, Benzo (g,h,i) perylene; DBA, Dibenzo (a,h) anthracene; IPY, Indeno (1,2,3-cd) pyrene.

3.3. Estimated relationship of PM$_{2.5}$ constituents with renal function

Fig. 2 illustrated the estimated changes in renal function indicators altered by ave 0–3 concentrations of trace metals and PAHs in PM$_{2.5}$. Among the 10 metal (metalloid) constituents, short-term exposure to Sb, As, Cd, Pb, Se and Ti were related to increased BUN and BUN/sCr. For example, an IQR increment in Cd (1.02 ng/m$^3$) was associated with 0.65 mmol/L increase in BUN (95% CI: 0.26 to 1.02) and 2.36 increase in BUN/sCr (95% CI: 0.75 to 3.89). The effects of each IQR increment in Pb (47.72 mmol/L) on BUN and BUN/sCr were 0.90 mmol/L (95% CI: 0.28 to 1.51) and 3.42 (95% CI: 0.84 to 5.89), respectively. Besides, PAHs of Chrysene, Benzo (a) anthracene, Benzo (a) pyrene and IPY in PM$_{2.5}$ were also positively associated with BUN and BUN/sCr. For example, an IQR increment in IPY (0.30 ng/m$^3$) were associated with 0.90 mmol/L (95% CI: 0.36 to 1.41) and 3.21 (95% CI: 0.97 to 5.34) higher of BUN and BUN/sCr, respectively. The relationships between the other 4 renal function indicators and the 26 PM$_{2.5}$ constituents were insignificant.

3.4. Mediation analysis

We explored the association between PM$_{2.5}$ and potential mediators through LME models (Table 3). Each IQR increments in PM$_{2.5}$ were associated with 1.64 U/mL (95% CI: 0.08 to 3.20) and 2.40 U/mL (95% CI: 0.37 to 4.42) increase in SOD at ave 0–2 and ave 0–3, respectively. The effects of PM$_{2.5}$ exposure on IL-6, hscRP, ACE and FIB were insignificant. Therefore, we further examined whether SOD could be a mediator of the associations between PM$_{2.5}$ and renal function. It was estimated that SOD contributed to 18.24% of the associations between PM$_{2.5}$ exposure and increased BUN at ave 0–3 (Fig. 3). Specifically, the NIE of PM$_{2.5}$ (each 32.94 μg/m$^3$ increase) on BUN was 0.08 mmol/L (95% CI: 0.01 to 0.16) at ave 0–3, while the NDE of PM$_{2.5}$ was 0.34 mmol/L (95% CI: 0.01 to 0.66).

3.5. Sensitivity analysis

A series of sensitivity analyses were conducted to check the robustness of our results. Firstly, we examined the time-varying confounding assumption using LME models, and found that there was insignificant association between BUN$_{ij}$ and SOD$_{ij}$ (Table S1). Additionally, we adjusted the other gaseous air pollutants into the two-pollutant LME models (Fig. S3), and the positive associations of PM$_{2.5}$ with BUN and BUN/sCr were significant. Moreover, we adjusted the PM$_{2.5}$ in the “constituent-PM$_{2.5}$ joint models” (Fig. S4A) and controlled the residual constituents of the total mass concentrations in the “constituent-PM$_{2.5}$ residual models” (Fig. S4B). We found relatively robust association between As, Cd, Pb, Se, Ti and IPY on BUN levels in both of two models.

4. Discussion

The research evaluated the adverse effect of PM$_{2.5}$ and its trace constituents on renal function parameters over a period of 3 days among 35 healthy young adults. After adjusting for several potential covariates, PM$_{2.5}$ mass concentrations and its several metals (metalloids) and PAHs showed strong associations with increased BUN and BUN/sCr. Additionally, we found elevated SOD levels due to PM$_{2.5}$ exposure may mediate the association between PM$_{2.5}$ exposure and renal functions. Our findings indicate that short-term exposure to PM$_{2.5}$ may increase the risks of renal dysfunction via systemic oxidative stress, in which the constituents of Pb, Cd, As, Se, Ti and IPY may play the leading roles.

Numerous studies provided epidemiological evidence that PM$_{2.5}$ may serve as a risk factor of renal dysfunction (Mehra et al., 2016; Tavera Buasso et al., 2018; Liu et al., 2020; Rahmani Sani et al., 2020; Zhao et al., 2020; Li et al., 2021). Most studies reported the significant associations between PM$_{2.5}$ and the kidney indicators of sCr and eGFR among populations. A recent panel study on 135 children aged 4–13 years reported that a 10 μg/m$^3$ increment of PM$_{2.5}$ was related to...
1.83% changes in eGFR (Liu et al., 2020). The VA Normative Aging Study reported that per 2.1 \( \mu g/m^3 \) increment in annual average of PM\(_{2.5}\) was related with 1.87 mL/min/1.73 m\(^2\) declination of eGFR among 669 older adults with an average age of 73.5 (Mehta et al., 2016). Another research reported that exposure to PM\(_{2.5}\) has a negative impact on renal function with 0.03 mg/dL increase in sCr and 1.09 mL/min/1.73 m\(^2\) reduction in eGFR among 150 pregnant women (Rahmani Sani et al., 2020). However, the associations of sCr and eGFR with PM\(_{2.5}\) were insignificant in this current research. This might be explained that children, the elderly and pregnant women were more vulnerable to the acute effects of PM\(_{2.5}\) on kidney than the healthy young adults in this study (Peled, 2011; Mukherjee and Agrawal, 2018).

The BUN, an end product of protein metabolism, was synthesized from amino acid metabolites in the liver and excreted from kidney. A cross-sectional study on pregnant women reported that for per 3.9 \( \mu g/\text{day} \) increase in PM\(_{2.5}\), there was a 0.03 mg/dL increase in sCr and a 1.09 mL/min/1.73 m\(^2\) reduction in eGFR (Liu et al., 2020). The VA Normative Aging Study reported that per 2.1 \( \mu g/m^3 \) increment in annual average of PM\(_{2.5}\) was related with a 1.87 mL/min/1.73 m\(^2\) decline in eGFR among 669 older adults with an average age of 73.5 (Mehta et al., 2016). Another research reported that exposure to PM\(_{2.5}\) has a negative impact on renal function with 0.03 mg/dL increase in sCr and 1.09 mL/min/1.73 m\(^2\) reduction in eGFR among 150 pregnant women (Rahmani Sani et al., 2020). However, the associations of sCr and eGFR with PM\(_{2.5}\) were insignificant in this current research. This might be explained that children, the elderly and pregnant women were more vulnerable to the acute effects of PM\(_{2.5}\) on kidney than the healthy young adults in this study (Peled, 2011; Mukherjee and Agrawal, 2018).

Fig. 1. Changes in renal function indicators (mean and 95% confidence intervals) with an interquartile range increment of PM\(_{2.5}\) in different exposure windows. (A) BUN, blood urea nitrogen; (B) sCr, serum creatinine; (C) UA, urea acid; (D) eGFR, estimated glomerular filtration rate; (E) Ccr, endogenous creatinine clearance rate; (F) BUN/sCr, blood urea nitrogen-to-serum creatinine. *Estimated were statistically significant (p-value < 0.05).

Fig. 2. The cumulative changes (mean and 95% confidence intervals) in renal function indicators associated with an interquartile range increment of 3-day moving average of PM\(_{2.5}\)-bound components. Abbreviations same as in Table 2 and Fig. 1. *Estimated were statistically significant (p-value < 0.05).

Table 3

| Changes in potential mediators (mean and 95% confidence intervals) associated with an interquartile range increment of PM\(_{2.5}\) in different exposure windows. |
|------------------|------------------|------------------|
|                  | ave 0–1 days     | ave 0–2 days     | ave 0–3 days     |
| SOD              | 1.51 (0.72, 3.24)| 1.64 (0.80, 3.20)*| 2.40 (0.37, 4.42)*|
| IL-6             | −0.05 (−0.33, 0.22) | −0.06 (−0.30, 0.19) | −0.09 (−0.37, 0.19) |
| hsCRP            | −0.06 (−0.18, 0.07) | −0.05 (−0.16, 0.05) | −0.07 (−0.20, 0.06) |
| FIB              | 0.00 (0.00, 0.04) | 0.01 (0.05, 0.03)  | 0.01 (0.05, 0.03)  |
| ACE              | 0.14 (0.49, 0.75)*| 0.14 (0.40, 0.68) | 0.21 (0.42, 0.84)  |

*Estimated were statistically significant (p-value < 0.05). Abbreviation: SOD, superoxide dismutase; FIB, fibrinogen; hsCRP, hypersensitive C-reactive protein; ACE, angiotensin converting enzyme; IL-6, interleukin-6.

−1.83% changes in eGFR (Liu et al., 2020). The VA Normative Aging Study reported that per 2.1 \( \mu g/m^3 \) increment in annual average of PM\(_{2.5}\) was related with 1.87 mL/min/1.73 m\(^2\) decline in eGFR among 669 older adults with an average age of 73.5 (Mehta et al., 2016). Another research reported that exposure to PM\(_{2.5}\) has a negative impact on renal function with 0.03 mg/dL increase in sCr and 1.09 mL/min/1.73 m\(^2\) reduction in eGFR among 150 pregnant women (Rahmani Sani et al., 2020). However, the associations of sCr and eGFR with PM\(_{2.5}\) were insignificant in this current research. This might be explained that children, the elderly and pregnant women were more vulnerable to the acute effects of PM\(_{2.5}\) on kidney than the healthy young adults in this study (Peled, 2011; Mukherjee and Agrawal, 2018).

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glomerular filtration, which in turn increases the burden of renal function. Concentrations after PM exposure to amino acids, which in turn caused increases of BUN generation (Macedo et al., 2021). The oxidative stress and inflammatory responses might increase the catabolism of structural proteins and amino acids, which in turn caused increases of BUN generation (Macedo et al., 2021).

The adverse effect of PM2.5 may affect renal function among healthy young adults. Several metal (metalloid) and PAHs components of PM2.5, such as Pb, Cd, As, Se, TI and IPY, might contribute to the observed association between PM2.5 and renal function. Additionally, our findings suggested that oxidative stress may be a plausible pathway which mediate the association between PM2.5 and renal dysfunction. The adverse effect of PM2.5, especially traffic-related particulate matters on renal function should be given more attention. Further studies are needed to verify our findings and elucidate the underlying mechanisms.

5. Conclusion

The current panel study provided the evidence that short-term exposure to PM2.5 may affect renal function among healthy young adults. Several metal (metalloid) and PAHs components of PM2.5, such as Pb, Cd, As, Se, TI and IPY, might contribute to the observed association. Additionally, our findings suggested that oxidative stress may be a plausible pathway which mediate the association between PM2.5 and renal function. The adverse effect of PM2.5, especially traffic-related particulate matters on renal function should be given more attention. Further studies are needed to verify our findings and elucidate the underlying mechanisms.
Author contribution
Shouxin Peng: Data curation, Methodology, Formal analysis, Writing – original draft, Visualization. Tianjun Lu: Validation, Writing – review & editing. Visi Liu: Validation, Writing – review & editing. Zhaoyuan Li: Methodology, Investigation, Software. FeiLei Liu: Investigation, Data curation, Software. JinHui Sun: Data curation, Software. Meijin Chen: Investigation. HuiJai Wang: Conceptualization, Investigation, Methodology. Hao Xiang: Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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