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Air pollution mixture associated with oxidative stress exacerbation and symptoms deterioration in allergic rhinitis patients: Evidence from a panel study

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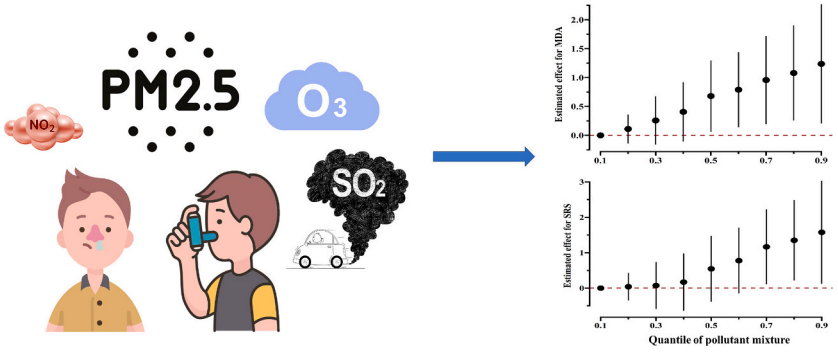
GRAPHICAL ABSTRACT



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ABSTRACT

With allergic rhinitis (AR) on the rise globally, there has been a growing focus on the role of environmental pollutants in the onset of AR. However, the potential mechanisms by how and which these pollutants exacerbate AR conditions remain unknown. This panel study of 49 patients diagnosed with AR over one year aimed to assess the individual and combined effects of short-term exposure to multiple ambient pollutants on oxidative stress, symptoms, and quality of life among patients with AR. All participants underwent four repeated assessments of health conditions and personal environmental exposures ($PM_{2.5}$, O_3, SO_2, and NO_2) over warm and cold seasons during 2017–2018. We evaluated two oxidative stress biomarkers (malondialdehyde [MDA], and superoxide

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dismutase [SOD]) via nasal lavage. We collected information on self-reported symptoms and quality of life using the Rhinitis Symptom Scale (SRS), the Visual Analog Scale (VAS), and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) through in-person interviews. Bayesian kernel machine regression (BKMR) was used to evaluate the joint effects of pollutant mixture and identify key contributors. The results revealed a significant association of the pollutant mixture when all four pollutants were at or above their median levels, with increased oxidative stress. This was evidenced by elevated MDA and reduced SOD. We found a joint detrimental effect of the pollutant mixture on AR symptoms with a strong association with increased SRS scores, but a non-significant positive association with VAS and RQLQ scores. $PM_{2.5}$, O_3, and SO_2 presented as the potentially primary contributors to the adverse health effects associated with the pollutant mixture in Taiyuan city. Patients with AR exposed to short-term air pollutant mixture are more likely to have greater nasal symptoms and worse quality of life from increased oxidative stress and reduced antioxidant capacity. Further research is warranted to better elucidate the underlying mechanisms.

1. Introduction

Allergic rhinitis (AR), has become increasingly prevalent worldwide, especially in developed and industrialized countries, with the prevalence rising from <1 % in the 1920s to 10–40 % in recent years (Jia et al., 2023; Zhang and Akdis, 2022). The characteristics of AR, including chronic nature, severeness, and recurrent manifestations, lead to reduced quality of life and impose a substantial burden on healthcare resources (Jia et al., 2023; Zhang and Akdis, 2022). In China, AR incidence with increased tendency has also been observed in the past a few years. It has been reported that self-reported and physician-diagnosed AR cases have been steadily rising, with a prevalence of 32.4 % of individuals self-reporting AR and 18.5 % receiving a physician-diagnosed AR in the northern region in 2009–2010 (Wang et al., 2016; Wang et al., 2018). AR not only significantly impacts an individual's quality of life but is also associated with other health conditions, including bronchial asthma, sinusitis, nasal polyps, otitis media, and allergic conjunctivitis (Naclerio et al., 2020; Kim et al., 2019).

The complete etiology and mechanisms for the development and exacerbation of AR are not yet understood. Several putative factors, such as ambient pollution, have been proposed, in addition to the increase in exposure to allergens (Passali et al., 2018). The rapid industrialization of China, accompanied by escalating environmental pollution, and the increasing prevalence of AR, highlights the need to elucidate the relationship between ambient air pollutants and the development of AR, which contributes to alleviating the corresponding health-related adversities. A growing body of evidence has explored the association between AR onset and ambient air pollutants such as fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) (Burte et al., 2018; Lee et al., 2003; Min et al., 2020; Li et al., 2022b; Chen et al., 2018). The potential mechanisms, notably oxidative stress, could shed light on the connections between air pollution and AR (Naclerio et al., 2020). In addition, pollen/protein might modify the advent of allergies and exacerbation of allergic symptoms due to air pollution, as some pollen proteins (e.g., birch pollen proteins) can be efficiently nitrated in polluted air, and subsequent posttranslational modification of proteins can potentially trigger immune responses (Franze et al., 2005; Reinmuth-Selzle et al., 2017). Nevertheless, it remains unclear whether the increased exposure to air pollutants continues to exacerbate the oxidative stress levels in AR patients, subsequently leading to more severe symptoms and a diminished quality of life. In addition, most previous studies have estimated the health effects of individual air pollutants, however, the potential synergistic or antagonistic effects resulting from pollutant mixtures could yield distinct implications for health outcomes in patients with AR (Dominici et al., 2010).

Due to the absence of curable treatments for AR, to date, it is important to prioritize the alleviation of their symptoms and the enhancement of quality of life. Therefore, we investigated individual and joint effects of short-term exposure to air pollutants ($PM_{2.5}$, SO_2, NO_2, O_3) with oxidative stress, subjective symptoms, and quality of life in individuals with AR.

2. Methods

2.1. Study design and population

We conducted a panel study involving individuals diagnosed with AR for at least one year in Taiyuan, a major industrial provincial capital in North China known for its severe air pollution (Wang et al., 2023). We carried out four repeated assessments of both health and environmental factors during both the warm (non-heating) and cold (heating) seasons from 2017 to 2018. We recruited study participants with clinically confirmed AR at Shanxi Provincial People's Hospital according to the guidelines for the Diagnosis and Treatment of Allergic Rhinitis in China (2015, Tianjin, China). The recruitment process involved a preliminary screening questionnaire, a skin prick test to assess allergic reactions, positive outcomes in allergic profile examination, and a comprehensive clinician examination conducted by medical professionals.

We conducted a meticulous exclusion process to ensure the integrity and accuracy of our study. Active smokers, individuals with long-term medication use (nasal corticosteroids, oral antihistamines, leukotriene modifiers, nasal antihistamines, etc.), occupational exposure (organic matters, dust, etc.), residence outside Taiyuan, or missing follow-up were all excluded from the study, culminating in a final of 49 participants for analyses. Ethical approval for this study was granted by the Ethics Committee of Shanxi Province People's Hospital, and all participants provided informed consent prior to their recruitment.

2.2. Assessment of ambient air pollutant exposure ($PM_{2.5}$, O_3, SO_2, NO_2)

This study focused on major air pollution that are routinely monitored, including $PM_{2.5}$, coarse particulate matter (PM_{10}), O_3, SO_2, NO_2, carbonic monoxide (CO). PM_{10} is not included in this analysis since $PM_{2.5}$ constitutes a subset of PM_{10}, rendering it inappropriate to simultaneously consider both as distinct pollutant components in the mixture analysis. Given that a recent meta-analysis showed no significant association between CO exposure and allergic rhinitis (Li et al., 2022b), CO was not taken into consideration for the analyses. Based on the referring the investigation of the spatial and temporal characteristics of air pollution and available literature about the air pollen content in Taiyuan during 2013–2016 (Tang et al., 2014, M Ferm et al., 2015), this study chose to conduct four repeated measurements of air pollution ($PM_{2.5}$, O_3, SO_2, and NO_2): twice in the warm season (June ~ August 2017) and twice in the cold season (December 2017 ~ January 2018). The collection times were chosen to avoid the peak season for allergens in Taiyuan, which typically occurs in August and September, coinciding with higher AR incidence. Data on daily $PM_{2.5}$, O_3, SO_2, and NO_2 measurements were obtained from eight monitoring stations across six urban districts in Taiyuan (Jiancaoping, Xinghualing, Wanbailin, Yingze, Jinyuan, and Xiaodian Districts) through China National Environmental Monitoring Center (http://www.cnemc.cn/). Furthermore, daily average ambient temperatures were acquired from the China Meteorological Data Sharing System (http://data.cma.cn/).

For each of the four measurement periods, the moving average of

each pollutant during 0–1 days ($lag_{0–1}$) prior to the date of follow-up visits was used to evaluate personal exposure level. For the O_3, SO_2, and NO_2, their pollutant concentrations from the monitoring station closest to participants' residential addresses were used as proxies for personal exposure. For $PM_{2.5}$, we applied the time-microenvironment-activity method to assess personal exposure (Schweizer et al., 2007), which takes into account a range of factors, including outdoor and indoor $PM_{2.5}$ concentrations, various microenvironments, and the daily activity patterns of participants. Additional details regarding the assessment of personal $PM_{2.5}$ exposure are shown in the Supplementary material appendix 1.

2.3. Assessment of oxidative stress, severity of symptoms, and quality of life

To assess oxidative stress, we measured parameters of malondialdehyde (MDA) and superoxide dismutase (SOD) of lavage biosamples from each participant, reflecting oxidative stress level and antioxidant enzyme activity (Camkurt et al., 2017). During each follow-up visit, we obtained nasal lavage fluid samples from each participant as follows: 1) participants were seated and instructed to gently open their mouths, briefly hold their breath, and instill 5 ml of saline solution into one of their nasal cavities; 2) after 10 s, participants were guided to tilt their heads to facilitate the collection of the lavage fluid, which was then collected in specialized centrifuge tubes; 3) subsequently, each participant repeated steps 1 and 2 for the other nasal cavity; 4) the centrifuge tubes containing the lavage fluid were then subjected to centrifugation and the resulting supernatant was stored at −40 °C. All experimental steps were executed in accordance with the instructions provided by the kits obtained from Nanjing Jianguo Bioengineering Institute, China.

To collect information on the participants' demographic characteristics, allergic rhinitis symptoms, severity, and consequent impact on quality of life, trained nurses conducted in-person interviews using a standardized questionnaire. The questionnaire includes demographics, details pertaining to the living environment, lifestyle factors, AR symptoms, and life quality assessment via the scores of three health scales, including 1) the Allergic Rhinitis Symptom Scale (SRS, scoring 0–3) for assessing the patients' nasal symptoms (Song and J., 2020); 2) the Visual Analog Scale (VAS, scoring 0–10) for evaluating the intensity of both patients' nasal and ocular symptoms (Doulaptsi et al., 2018); and 3) the Rhinitis Related Quality of Life Scale (RQLQ, scoring 0–6) for patients' quality of life (Meltzer, 2001). Both higher SRS and VAS scores indicate worse symptoms, and a higher RQLQ score indicates a diminished quality of life.

2.4. Covariates

We collected demographic information, residential environment details, and lifestyle data through the three structured questionnaires for all measurement periods. In alignment with our prior research, the following covariates were considered to control for confounding factors: age (≤35 years vs. >35 years), gender (male vs. female), BMI (<24 vs. ≥24), smoking status of family members inside the house (yes vs. no), frequency of alcohol consumption per week (never vs. 1–2 times vs. 3–7 times vs. > 7 times), usage of other medications (yes vs. no), presence of pets (yes vs. no), physical activity level from questionnaire surveys (never vs. light level vs. medium level vs. high level), cooking behaviors (patient-self vs. other family members), time elapsed since the last house renovation (< 2 years vs. ≥2 years), frequency of window ventilation in both bedroom and living room (< 10 % vs. 11–20 % vs. 21–50 % vs. > 50 %), humidifier usage (yes vs. no), ambient allergen score (0–3 scores), and ambient temperature during 0–1 days ($lag_{0–1}$) prior the date of follow-up visits.

To account for potential allergic effects, we calculated an ambient allergen score based on three key ambient allergens that contributed to allergic rhinitis in northern China (dust mites, artemisia, and pollen) (Gao et al., 2019; Li et al., 2009). Each exposure to these allergens added a score of 1 for each participant. The cumulative score, ranging from 0 to 3, serves as a measure of the overall ambient allergen exposure level for each participant (**Supplementary Material Appendix 2**).

2.5. Statistical analysis

For the descriptive analyses, we used the mean ± standard deviation (SD) to summarize continuous variables. To standardize pollutant concentrations, we represented each pollutant exposure as centered z-scored continuous variables. Regarding the outcomes, both MDA and SOD did not follow a normal distribution and were therefore modeled as Box Cox-transformed and then z-scored continuous variables. Conversely, SRS, VAS, and RQLQ exhibited right-skewed distributions and were modeled as natural log-transformed and then z-scored continuous outcomes.

For multi-pollutant analysis, Bayesian kernel machine regression (BKMR) with random intercept method (Bobb et al., 2018; Bobb et al., 2015) was applied to estimate individual and joint effects of exposure to air pollutants on MDA, SOD, SRS, VAS, and RQLQ. The BKMR method could comprehensively assess the joint effects, potential interactions, and nonlinear and nonadditive effects of air pollutants through multivariable exposure-response functions. A distinctive attribute of BKMR is its flexible modeling of the exposure-response relationship, which eliminates the necessity for predefined a priori (e.g., utilizing a quadratic term). The formula of BKMR is as follows:

$$Y_i = h(PM_{2.5i}, O_{3i}, SO_{2i}, NO_{2i}) + \beta^T Z_i + \varepsilon_i \quad (1)$$

Where function $h()$ is the exposure-response function accommodating nonlinearity and/or interactions among the pollution mixture components, Z represents covariates and ε represents residual term. In this context, defining a set of basic functions, such as spline or polynomial terms, for representing $h()$ poses challenges. For instance, employing a spline basis with three degrees of freedom (df) to accommodate nonlinearity and interactions among 4 pollutants necessitates estimating 255 parameters [generally $(1+df)^m - 1$ parameters for m mixture components]. BKMR addresses the complexity inherent in the high-dimensional parameter space of the exposure-response function by adopting a kernel machine approach for $h()$. The kernel machine reformulates the model as a linear mixed model, facilitating regularization of the estimated exposure-response function and offering multiple computational benefits (Bobb et al., 2015). In this study, we employed the Gaussian kernel, known for its versatility in capturing diverse functional forms for $h()$, and proven effectiveness in simulation studies that mimic realistic exposure-response scenarios (Bobb et al., 2015). Fitting BKMR not only provides estimates of $h()$ but also its associated uncertainty. BKMR also enables the derivation of summary statistics from the model fit, which illuminates scientifically significant attributes of the exposure-response function, facilitating an understanding of the combined effects of the mixture. The credible intervals derived from the BKMR model fitting reflect the added uncertainty stemming from estimating a set of exposures, thereby addressing the multiple-testing penalty (Scott and Berger, 2010). Furthermore, BKMR incorporates the component-wise or hierarchical variable selection method to discern critical components of pollutant mixture and accommodate its correlated structure.

Applying BKMR, we investigated as follows: 1) the joint effects of pollution mixture on outcomes via estimating outcome changes related to concurrent increases in all pollutants of the mixture from their 10th quantile level to 90th quantile level; 2) the individual effects of per interquartile range (IQR) increment of each pollutant on outcomes and possible interactions among pollutants via setting the remaining pollutants at the 25th, 50th, and 75th quantile levels, respectively; 3) the pollutant-specific nonlinear exposure-response functions with the remaining pollutants fixed at the median; 4) the variable-specific

posterior inclusion probability (PIP) for each pollutant using component-wise variable selection, which represents the probability that a pollutant of the mixture was included in the BKMR model. A PIP value surpassing 0.5 is a reliable indicator of predicting outcomes (Li et al., 2022a).

We adjusted the model for all covariates mentioned above. Given that different types of allergies potentially exist, and some might exert an impact on the effect estimation of pollutant mixture, we have additionally conducted a sensitivity analysis by adjusting for allergy types (seasonal vs. perennial).

All statistical analyses were performed using R software version 4.1.3 (R Development Core Team), and we considered a two-tailed $P < 0.05$ for statistical significance.

3. Results

From June 2017 to January 2018, a number of 49 participants ($n = 49$) with four repeated measurements were included in this study. The average age of participants was 36.7 years old (SD: 8.4y), ranging from 23 to 59 years. Approximately 75.5 % of them were female, and 32.7 % had a BMI exceeding 24 kg/m^2 (**Supplementary Table S1**). Table 1 shows the mean (SD) values of 2-day moving average pollutant exposure, oxidative stress parameters, and scores of three health scales. The highest personal exposure to $PM_{2.5}$ (65.2 μg/m^3), SO_2 (121.6 μg/m^3), and NO_2 (73.1 μg/m^3) occurred simultaneously in the last measurement in January 2018, while the highest O_3 exposure (92.6 μg/m^3) was observed in the first measurement in June 2017. Mean MDA ranged from 3.6 to 6.5 nmol/ml, and mean SOD ranged from 97.1 to 111.5 U/ml, with highest MDA but lowest SOD recorded in the last measurement. The lowest mean values for SRS, VAS, and RQLQ were all observed in June 2017. Other time-varying characteristics of the study subjects at each measurement are displayed in **Supplementary Table S2**.

Figs. 1 and Fig. 2 illustrate the findings regarding the overall and individual effects of $PM_{2.5}$, O_3, SO_2, and NO_2 on oxidative stress parameters (MDA and SOD). In Fig. 1A, we observed a positive association between exposure to pollutant mixture and MDA levels. Specifically, MDA significantly increased when all four pollutants were at or above their median levels, compared to when they were all at their lowest quantile. Among these pollutants, $PM_{2.5}$ displayed the strongest consistent positive association with MDA (*Z*-scored). In Fig. 1B, $PM_{2.5}$ exposure demonstrated a positive, though not statistically significant, association with an increase with an IQR increase in MDA (Z-scored) when O_3, SO_2, and NO_2 remain at their respective 25th, 50th, and 75th quantiles. Fig. 1C presents the exposure-response relationship for each pollutant when others are held constant at the 50th quantiles, suggesting positive monotonic correlations between $PM_{2.5}$, O_3, and SO_2 with MDA, albeit estimates crossed the null. In Fig. 2A, SOD decreased as the pollutant mixture increased from the 10th quantile to the 90th quantile. However, this joint effect was less pronounced than with MDA, with a statistically significant difference only at the 70th and 80th quantiles of the four pollutants; the effect estimate of 90th trended downwards as well, but there was way more variability in the estimate, which led its upper limit of the confidence interval to cross the null value. Furthermore, with an IQR increase in each individual pollutant while other pollutants are fixed at the 25th, 50th, and 75th percentiles, no significant associations between each pollutant exposure level and the SOD expression, irrespective of the concentrations of other pollutants (Fig. 2B). Besides, Fig. 2C indicates the univariate exposure-response functions for primary analysis, which shows the association between each pollutant and SOD (z-scored) when all the other pollutants are fixed at the 50th percentile.

Figs. 3 and Fig. 4 depict the joint and individual effects of $PM_{2.5}$, O_3, SO_2, and NO_2 on subjective symptoms score (SRS and VAS) and quality of life (RQLQ) among AR patients. We observed a significant positive association between an increment in pollutant mixture and SRS scores, while it tended to be positively but non-significantly correlated with VAS and RQLQ. The joint toxic effect of the mixture on SRS was statistically significant when all components of the mixture were at or above the 70th quantile. The single-pollutant associations suggested an interaction with other pollutants (**Fig. S1**). In Fig. 4, SRS, VAS, and RQLQ exhibited approximately positive trend of linear correlations with O_3 and SO_2 but displayed a non-monotonic correlation with $PM_{2.5}$.

Table S1 provides the PIP (ranging from 0 to 1) for each pollutant, indicating their relative posterior probability that a specific mixture component is included in the final model. For all outcomes, $PM_{2.5}$, O_3, and SO_2 had a PIP larger than 0.5, serving as reliable indicators of predicting outcomes. The results of sensitivity analysis show that joint effect estimations by additionally adjusting for allergy types were consistent with that from the main analysis (**Fig. S2**).

4. Discussion

In this study, we investigated associations between short-term exposure to an ambient air pollutant mixture and AR symptoms and nasal biomarkers. We found evidence of the individual, interactive, and joint effect of personal exposure to ambient air pollution mixture ($PM_{2.5}$, O_3, SO_2, and NO_2) on oxidative nasal biomarkers, AR symptoms, and quality of life among AR patients. Our findings highlight the joint acute effects of exposure to air pollutant mixture on the exacerbation of oxidative stress (MDA, SOD) and nasal symptoms (SRS).

4.1. Previous findings

As a bothersome condition, AR significantly impacts patients' quality of life, sleep patterns, work productivity, and overall daily activities (Li et al., 2022b). There is growing evidence for higher AR prevalence in high air pollutant areas (Burte et al., 2018; Lee et al., 2003; Min et al., 2020; Li et al., 2022b), Although the association has not been consistently affirmed across all relevant studies. Some studies have highlighted a close link between increased AR onset and air pollution exposure, particularly particulate matter (Dunlop et al., 2016; Luo et al., 2020) and O_3 (Bédard et al., 2020; Pénard-Morand et al., 2005); others have suggested a minimal association between AR and levels of air pollution (Fuertes et al., 2013; Gehring et al., 2015; Pindus et al., 2016). It has been reported that ambient pollutants induce oxidative stress and inflammatory responses, thus exacerbating allergic airway diseases (Guo et al., 2019; Naclerio et al., 2020). Nevertheless, limited information on the overall effects of multiple pollutants on oxidative stress,

Table 1
Summary statistics for exposures to air pollution during 0–1 days before measurement, oxidative stress markers and health scale scores *.

Measurement	n obs	Air pollution				Oxidative stress expression		Scores of the three health scales		
		$PM_{2.5}$ (μg/m^3)	O_3 (μg/m^3)	SO_2 (μg/m^3)	NO_2 (μg/m^3)	MDA (nmol/ml)	SOD (U/ml)	SRS	VAS	RQLQ
1	49	24.12 (3.9)	92.6 (10.5)	6.5 (0.9)	33.8 (4.9)	3.6 (1.1)	111.5 (18.0)	1.9 (2.3)	6.6 (9.9)	10.2 (16.2)
2	49	48.4 (4.41)	87.2 (3.4)	27.6 (11.7)	56.5 (8.0)	3.8 (1.3)	108.3 (17.0)	3.0 (2.4)	11.5 (11.4)	17.1 (19.5)
3	49	47.1 (8.3)	30.3 (4.4)	62.4 (20.9)	53.3 (5.3)	5.5 (1.2)	97.3 (12.8)	2.4 (2.4)	8.6 (9.1)	17.6 (22.1)
4	49	65.2 (6.8)	27.4 (5.6)	121.6 (18.1)	73.1(6.8)	6.5 (1.1)	97.1 (13.1)	2.2 (1.9)	8.5 (9.1)	12.5 (15.0)

Note: * All continuous variables were presented as mean (SD).

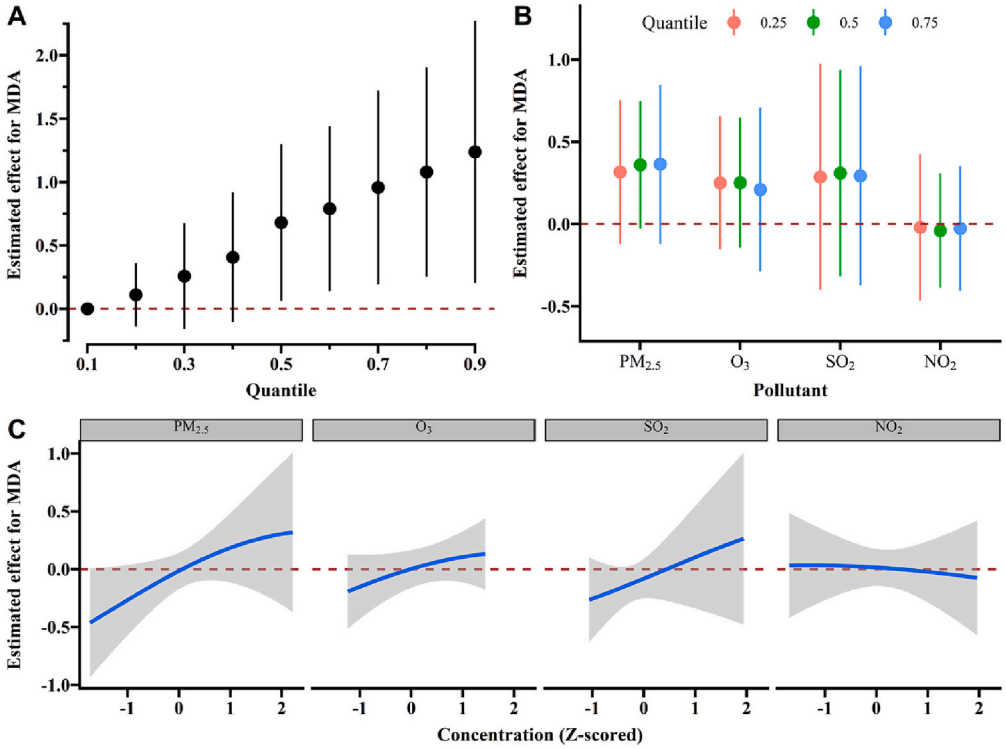

Fig. 1. The joint effect of air pollution mixture on malondialdehyde (MDA) of allergic rhinitis patients estimated by Bayesian Kernel Machine Regression (BKMR). The model was adjusted for age, gender, BMI, smoking status in the house, drinking frequency, medication usage, presence of pets, physical activity, cooking behaviors, time elapsed since the last house renovation, frequency of window aeration in both bedroom/living rooms, humidifier usage, ambient allergen score, and temperature. (A) Overall effect of pollutant mixture (estimates and 95 % confidence intervals). The plot displays the estimated shifts in MDA (*Z*-scored) when all pollutants were at specific quantiles (0.1 to 0.9) compared to when all were at their 0.1 quantiles. (B) Single-pollutant association (estimates and 95 % confidence intervals, red dash line at the null). The plot displays shifts in MDA (*Z*-scored) related to an interquartile range increment of a single pollutant, when other pollutants remained at the 0.25, 0.50, and 0.75 quantile levels, respectively. (C) Pollutant-specific exposure-response function and 95 % confidence band when other pollutants were fixed at the median.

disease severity, and quality of life in AR patients is available. Therefore, the current panel study could offer some preliminary evidence regarding this intricate association.

4.2. Impact of ambient pollutants on oxidative stress nasal biomarkers

We applied nasal lavage from participants using the methods we reported in the previous publication (Li et al., 2023). Compared to the bronchoalveolar lavage (BAL), the nasal lavage is a relatively less aggressive method that could be applied to hypersensitivity studies, especially for upper air way diseases. As for the reliability, reproducibility, and explanatory power of the nasal lavage method compared to BAL. The previous study on 10 volunteers who had acute oxidative air pollutant exposure compared the inflammatory response of upper airways using nasal lavage with lower airway response using BAL (Koren et al., 1990). The results approved that nasal lavage could play the role of a sensitive and reliable method in clinical practice to detect inflammation reactions and indicated that nasal lavage might mirror the inflammation response from the lower airway after choric exposure to pollutants. This shows the strong reliability and explanatory power of the nasal lavage method. Additionally, another study by Roberto Castano et al. explored the short-term reproducibility of inflammatory cells and cellular markers of occupational rhinitis in 25 participants and confirmed that nasal lavage showed sufficient reproducibility for detecting upper airway inflammation (Castano et al., 2008). Therefore, nasal lavage in this study could provide more valuable information for allergic rhinitis, an upper respiratory tract disease. However, some differences for specific upper- or lower-expression of proteins were only detected in BAL or nasal lavage biosamples from the study by Lindahl et al. (Lindahl et al., 1998), which indicated the application of these biosamples requires more support from clinical diagnosis and suspected lower- or upper- respiratory tract diseases.

According to our study of ambient pollution mixture using BKMR, we have found significant insights into the impact of overall pollution mixture on two primary inflammatory indices from nasal lavage samples of AR patients. Notably, our research highlights the synergistic effects of this mixture. Specifically, when comparing scenarios where each pollutant was at or above its median concentration to situations where all four pollutants were at their 10th percentile, we found a significantly positive joint association between pollution mixture and MDA levels. A prior study using a single-pollution model has reported that lag 1-day $PM_{2.5}$ exposure was related to evaluated MDA levels in AR patients (Yang et al., 2019). MDA, a byproduct of lipid peroxidation resulting from the assault of oxygen-free radicals on biomembranes, serves as an indirect indicator of cellular damage due to these radicals. Furthermore, this study reveals the decline in SOD levels, an antioxidant enzyme, in conjunction with increased exposure to the ambient pollutant mixture, and suggests a potential compromise in the body's antioxidative defense mechanisms. Oxidative stress, known to be implicated in various physiological and pathological conditions, has the potential to perturb the antioxidant system. This disruption may contribute to health detriments such as respiratory tract inflammatory diseases, which can ultimately impact the daily functionality and quality of life for AR patients (Han et al., 2021).

In addition, the estimated PIP values indicated the influence of all pollutants except NO_2, demonstrating a strong effect on the oxidative stress biomarkers, as indicated by PIP values exceeding 0.5. A PIP value surpassing 0.5 is a reliable indicator of the outcomes (Li et al., 2022a).

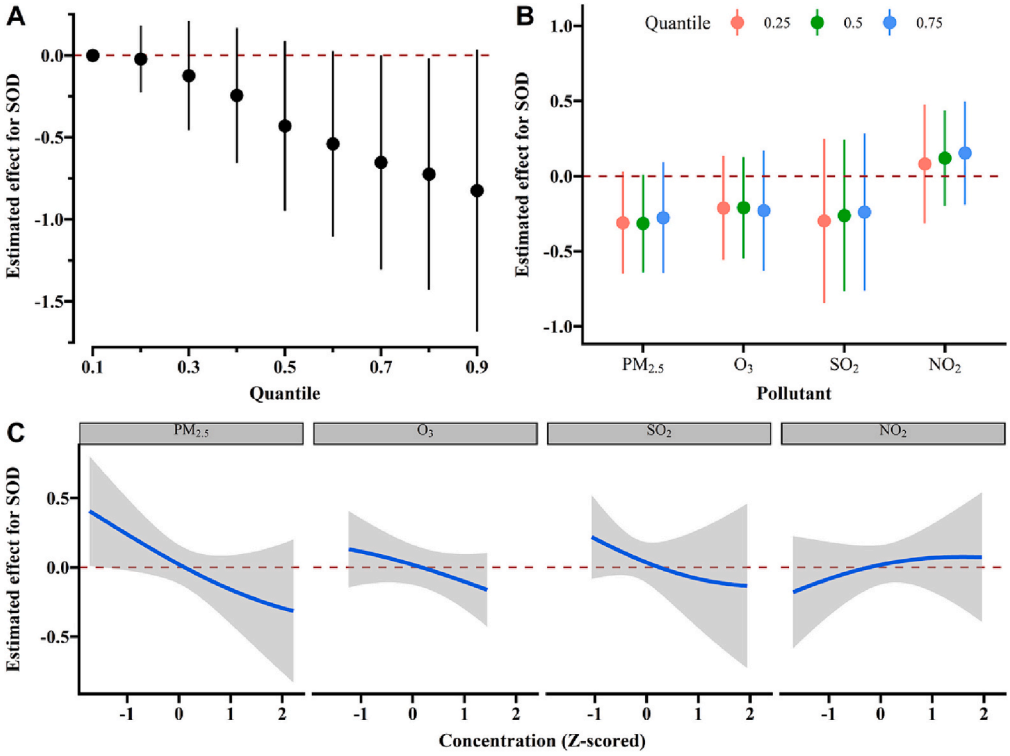

Fig. 2. The joint effect of air pollution mixture on superoxide dismutase (SOD) of allergic rhinitis patients estimated by Bayesian Kernel Machine Regression (BKMR). The model was adjusted for age, gender, BMI, smoking status in the house, drinking frequency, medication usage, presence of pets, physical activity, cooking behaviors, time elapsed since the last house renovation, frequency of window aeration in both bedroom/living rooms, humidifier usage, ambient allergen score, and temperature. (A) Overall effect of pollutant mixture (estimates and 95 % confidence intervals). The plot displays the estimated shifts in SOD (Z-scored) when all pollutants were at specific quantiles (0.1 to 0.9) compared to when all were at their 0.1 quantiles. (B) Single-pollutant association (estimates and 95 % confidence intervals, red dash line at the null). The plot displays shifts in SOD (Z-scored) related to an interquartile range increment of a single pollutant, when other pollutants remained at the 0.25, 0.50, and 0.75 quantile levels, respectively. (C) Pollutant-specific exposure-response function and 95 % confidence band when the remaining pollutants were fixed at the median.

The pollutant-specific exposure-response curves also showed that $PM_{2.5}$, O_3, and SO_2 were positively related to MDA and negatively related to SOD (Fig. 1C and 2C), which might be important contributors to the joint effects. Previous toxicological studies have explored the various biological mechanisms and molecular pathways regarding the influences of $PM_{2.5}$ exposure on the inflammatory response based on the AR mouse models. They reported that exposure to $PM_{2.5}$ could intensify oxidative stress responses via increasing MDA and reducing SOD levels (Piao et al., 2021; Wang et al., 2020b). High concentration of metal cations and polycyclic aromatic hydrocarbons (PAHs) in $PM_{2.5}$ have the potential to exacerbate Th2-dominant allergic inflammation in AR mice. This exacerbation may lead to redox imbalance, nasal epithelial cell desquamation, and eosinophil infiltration (Wang et al., 2020a), all of which might be the potential toxic mechanisms associated with $PM_{2.5}$ exposure. Additionally, mice models have demonstrated that increased exposure to O_3 could trigger the development of inflammation, including serum total levels of IgE and IgG1 (Immunoglobulin G 1) (Neuhaus-Steinmetz et al., 2000). SO_2 is widely recognized as an inducer of inflammation in the respiratory system (Wang et al., 2014), which potentially acts synergistically in airway allergy, amplifying allergic inflammation, and promoting the evolution of allergic immunity (Wang et al., 2020b). In contrast, although reports for the associations of NO_2 and biomarkers of traffic-related air pollutants with the risk of AR onset risk have been reported in Asia and Europe (Hwang et al., 2006; Wang et al., 2021; Cesaroni et al., 2008; Krämer et al., 2000), it's worth noting that the consistency of this association remains inconsistent across studies, and most previous studies focused solely on NO_2 without disentangling the effects of NO_2 from other co-pollutants (Li et al., 2022a). The WHO REVIHAAP project, which analyzed the health impacts of NO_2, found that it was challenging to isolate the specific effects of NO_2 due to its high correlation with other ambient pollutants (WHO, 2021). In this study, using a novel mixture method, BKMR, we simultaneously assess the effects of highly correlated exposure to obtain relatively robust estimates.

4.3. Detrimental effect on symptoms and quality of life

Our findings first revealed that short-term exposure to air pollutant mixture could exacerbate AR conditions, manifesting in a positive association with SRS and a non-significant positive association with VAS. Furthermore, the BKMR model in this study has contributed to identifying that the overall air pollution mixture was positively but non-significantly associated with evaluated RQLQ (indicating the lower quality of life) in AR patients. We cannot rule out the possibility that significant effects for VAS and RQLQ were not detected due to the limited sample size in this pilot study, individual perception differences, and reporting bias in the health scales of this study. Nevertheless, we have tried our best to follow up with the participants to collect reliable information. We would like to further explore the use of advanced methods such as Bootstrap in machine learning with statistical collaborators in future studies to yield robust and reliable results.

AR, characterized by typical symptoms such as nasal congestion, runny nose, paroxysmal sneezing, nasal itching, and ocular manifestations, has been consistently linked to the detriment of patients' quality of life (Blaiss et al., 2018; Bousquet et al., 2013). The results of overall effects, pollutant-specific exposure-response curves, single-pollutant association, and PIP for AR symptoms (SRS and VAS) and quality of life (RQLQ) followed a similar pattern. When other pollutants remained

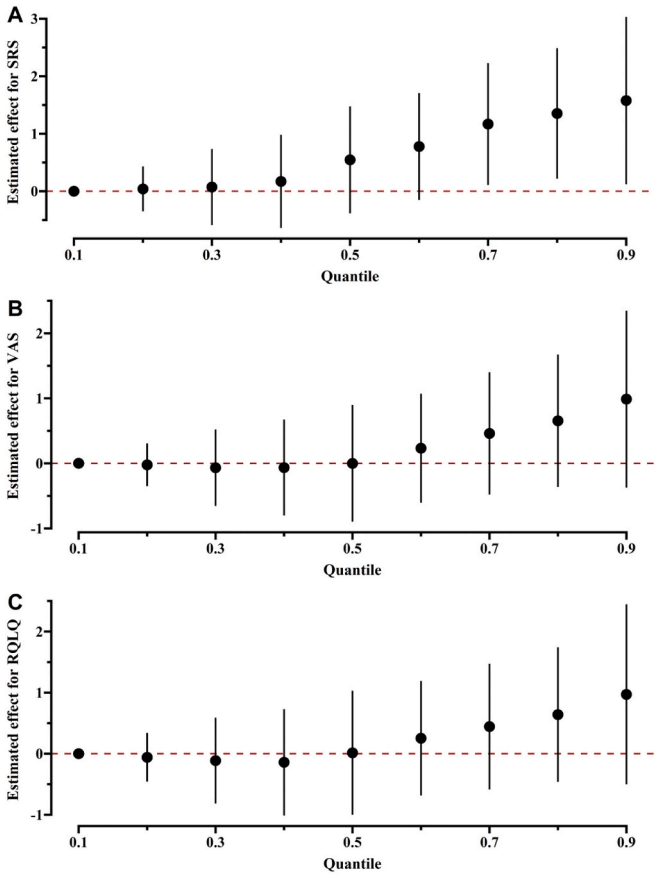

Fig. 3. The overall effect of air pollution mixture on allergic rhinitis patients' A) Allergic Rhinitis Symptom Scale (SRS), B) Visual Analog Scale (VAS), C) Rhinitis Related Quality of Life Scale (RQLQ), estimated by Bayesian Kernel Machine Regression (BKMR). The model was adjusted for age, gender, BMI, smoking status in the house, drinking frequency, medication usage, presence of pets, physical activity, cooking behaviors, time elapsed since the last house renovation, frequency of window aeration in both bedroom/living rooms, humidifier usage, ambient allergen score, and temperature. The plot displays the estimated shifts and 95 % confidence intervals in each outcome (z-scored) when all pollutants were at specific quantiles (0.1 to 0.9) compared to when all were at their 0.1 quantiles.

at the 0.50 quantile levels, the pollutant-specific exposure-response curves show a positive relationship of O_3, SO_2, and $PM_{2.5}$ with three outcomes except a non-linear association of $PM_{2.5}$ with SRS. Generally, O_3, SO_2, and $PM_{2.5}$ mainly drive the joint effects on AR symptoms and patients' quality of life. Our findings align with previous studies focused on single pollutant's effect assessment, in which the epidemiological data illustrating the role of ambient exposure to O_3 and SO_2 in triggering AR (Hsieh et al., 2020; Bédard et al., 2020). Additionally, well-conducted studies reported that exposure to $PM_{2.5}$ is associated with higher rhinitis severity in adults (Burte et al., 2020), exacerbation of subjective symptoms in children with AR (He et al., 2017), and evaluated risk of nonaccidental years of life lost (YLL, an indicator of life expectancy) (Yin et al., 2022).

Notably, joint effects of pollutant mixture on all targeted outcomes in this study were driven by the similar rank of pollutant contributors, as indicated by PIPs. This implies the existence of a potential evidence chain that the toxic environment pollution components might first exacerbate the inflammatory response in AR patients, subsequently intensify their subjective symptoms, and ultimately compromise their quality of life. It is plausible that oxidative stress plays a pivotal role as the key biological mechanism underlying the exacerbation of AR condition due to exposure to the air pollutants mixture. Additionally, a previous study has also revealed a relevant mechanism that air pollution can effectively accelerate the nitration of certain pollen proteins, the posttranslational modification of which may induce immune responses and exacerbate allergic symptoms (Franze et al., 2005). However, our understanding of this complex relationship remains incomplete and, therefore, warrants further investigation.

4.4. Strengths and limitations

To the best of our knowledge, this is the first epidemiological investigation on the joint effects of personal exposure to ambient air pollutant mixture on oxidative stress, subjective symptoms, and quality of life in AR patients. Our novel approach involved a panel study methodology encompassing four measurements among screened AR patients. This allowed us to collect comprehensive information and track changes in study participants' personal environmental exposures and health outcomes over time. By employing the BKMR model, we addressed significant shortcomings inherent in conventional analyses, including the estimation of individual pollutant effects, multi-collinearity of co-exposure, potential model misspecification, and higher possibility of false discovery with fitting numerous regression models.

This study has several limitations. First, exposure to O_3, SO_2, and NO_2 was estimated by the nearest air pollution monitoring station, which might cause measurement errors. Different from personal $PM_{2.5}$ exposure estimation, the assessments of personal exposure to O_3, SO_2, and NO_2 lacked time-microenvironment-activity information, which might have been less accurate than $PM_{2.5}$. Second, this fixed tracking group faced constraints in terms of sample size and the times of measurements because of the inherent challenges and substantial expenses associated with follow-up within the panel study design, highlighting the need for further investigations with a larger participant base to further strengthen the evidence. Third, a common limitation in panel studies is participant attrition, which has the potential to introduce bias. Despite our concerted efforts to minimize the incidence of loss to follow-up, this remained a challenge that must be acknowledged. Fourth, although we adjusted for key confounders such as ambient temperature, clinical history, living conditions, and main allergens, the possibility of unmeasured or residual confounding cannot be entirely ruled out. Fifth, this study lacked access to the detailed allergic profiles of participants, impeding our capacity to elucidate sensitizations to specific allergens among AR patients. However, our regression models did incorporate potential confounders linked to common allergenic sources, such as pets, cooking activities, home renovations, and environmental allergen scores (dust mites, artemisia, and pollen). Last, this panel study cannot rule out potential regulation from dietary effects on oxidative stress in AR patients, due to the absence of detailed dietary information. While it was assumed that participants had relatively consistent dietary habits, given the local dietary habits are undergoing substantial changes with rapid developments of society and urbanization, further research is needed to explore the interactive effects of diet on oxidative reactions in allergic disease patients exposed to diverse levels of air pollution. This would provide additional evidence to better understand the complex relationship between diet, air pollution, and oxidative stress in AR patients.

5. Conclusion

This is the first panel study to simultaneously focus on the associations of multiple air pollutants mixture with symptoms and quality of life in AR patients and potential mechanism, adding to the very limited existing evidence concerning the effects of short-term co-exposure to air pollutants on the deterioration of symptoms in AR patients and the potential function of oxidative stress. The implications of our findings hold the promise of providing new insights into the impacts of pollutants on AR patients. Maintaining air pollution levels, especially detrimental $PM_{2.5}$, O_3, and SO_2, below stricter thresholds, could potentially alleviate symptoms in AR patients and significantly enhance their quality of life.

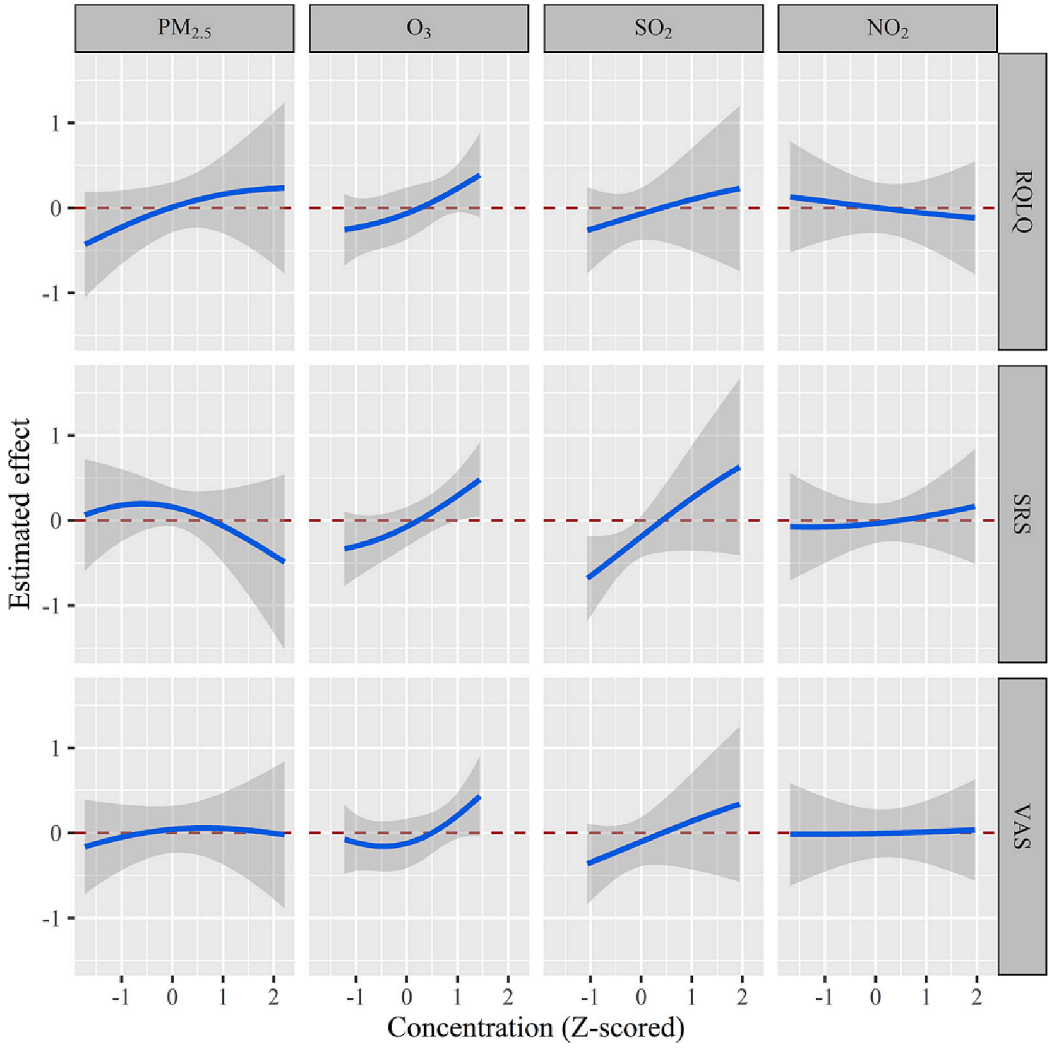

Fig. 4. Univariate exposure-response function and 95 % confidence band for each pollutant on allergic rhinitis patients' Allergic Rhinitis Symptom Scale (SRS), Visual Analog Scale (VAS), Rhinitis Related Quality of Life Scale (RQLQ), estimated by Bayesian Kernel Machine Regression (BKMR). The model was adjusted for age, gender, BMI, smoking status in the house, drinking frequency, medication usage, presence of pets, physical activity, cooking behaviors, time elapsed since the last house renovation, frequency of window aeration in both bedroom/living room, humidifier usage, ambient allergen score and temperature. The pollutant-specific effect was estimated via setting other pollutants at the median.

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CRediT authorship contribution statement

Jinhui Li: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Haisheng Wu:** Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Weiwei Xing:** Resources, Investigation, Data curation. **Xin Li:** Resources, Investigation, Data curation. **Zheshen Han:** Writing – review & editing. **Renyue Ji:** Writing – review & editing. **Zhengyi Deng:** Writing – review & editing. **Minji Jung:** Writing – review & editing. **Shengzhi Sun:** Writing – review & editing, Methodology, Conceptualization. **Benjamin I. Chung:** Writing – review & editing, Methodology, Conceptualization. **Andres Cardenas:** Writing – review & editing, Conceptualization. **Marvin E. Langston:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.172688.

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