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Increased allostatic load associated with ambient air pollution acting as a stressor: Cross-sectional evidence from the China multi-ethnic cohort study

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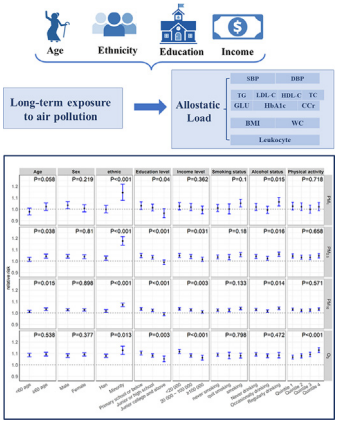
HIGHLIGHTS

- The relationship between AP and AL was estimated in adults with large sample sizes.
- Exposure to $PM_{2.5}$, PM_{10}, and O_3 were significantly associated with increased AL.
- The effect of AP on AL may be higher in elderly, minority, lower educated/income.
- AP may be a chronic stressor, leading to broad damaging effects on multiple organs.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Allostatic load measures the cumulative biological burden imposed by chronic stressors. Emerging experimental evidence supports that air pollution acting as a stressor activates the neuroendocrine system and then produces multi-organ effects, leading to allostatic load. However, relevant epidemiological evidence is limited.
Objectives: We aim to explore the relationships between chronic exposure to ambient air pollution (PM_1, $PM_{2.5}$, PM_{10}, and O_3) and allostatic load in Chinese adults.
Methods: This cross-sectional study included 85,545 participants aged 30–79 from the baseline data of the China Multi-Ethnic Cohort (CMEC). Ambient air pollution levels were evaluated by a satellite-based random forest approach. The previous three-year average exposure concentrations were calculated for each participant based on the residential address. The outcome allostatic load was identified through the sum of the sex-specific scores of twelve biomarkers

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belonging to four major categories: cardiovascular, metabolic, anthropometric, and inflammatory parameters. We performed statistical analysis using a doubly robust approach which relies on inverse probability weighting and outcome model to adjust for confounding.

Results: Long-term exposure to ambient air pollution was significantly associated with an increased risk of allostatic load, with relative risk (*95%* confidence interval) of 1.040 (1.024, 1.057), 1.029 (1. 018, 1. 039), and 1.087 (1.074, 1.101) for each 10 μg/m^3 increase in ambient $PM_{2.5}$, PM_{10}, and O_3, respectively. No significant relationship was observed between chronic exposure to PM_1 and allostatic load. The associations between air pollution and allostatic load are modified by some intrinsic factors and non-chemical stressors. The people with older, minority, lower education, and lower-income levels had a significantly higher allostatic load induced by air pollution.

Conclusions: Chronic exposure to ambient $PM_{2.5}$, PM_{10}, and O_3 may increase the allostatic load. This finding provides epidemiological evidence that air pollution may be a chronic stressor, leading to widespread physiological burdens.

1. Introduction

Ambient air pollution (AP) has been recognized as a significant public health hazard globally. Indeed, air pollution ranked fourth among risk factors for global attributable mortality, contributing to 6.67 million deaths in 2019 (GBD 2019 Risk Factors Collaborators, 2020). Over the past decades, the adverse effects of air pollution on specific organs or diseases have been well explored, primarily focusing on cardiometabolic (Brook et al., 2010; Simkhovich et al., 2008) and pulmonary diseases (C Arden et al., 2002; Sunyer, 2001) and, more recently, neurological and psychiatric disorders (Braithwaite et al., 2019; Jo et al., 2021). Considering the possible existence of common pathways among various diseases (such as inflammation and oxidative stress), it seems necessary to identify the broad effects of air pollution on multiple organs and systems. Such findings may be helpful in understanding the linkage of the complex pathogenesis in various air pollution-related diseases, and whether various diseases are driven by common initial events (Juster et al., 2010; Snow et al., 2018; Thomson, 2019). Furthermore, since many people suffer from a combination of multiple diseases (Jankovic et al., 2018; Wang et al., 2014; Zhao et al., 2021), such multimorbidity underscores the necessity to measure multi-organ or system effects induced by air pollution.

A key concept that helps to explain the multi-organ effects of air pollutants exposure is allostatic load (AL), which measures the cumulative biological burden caused by chronic exposure to stressors (McEwen and Stellar, 1993; Seeman et al., 1997; Seeman et al., 2001). Allostatic load is hypothesized to be a marker reflecting the cumulative biological effect of environmental and social stressors (pollutions and low socioeconomic status), individual major challenges (life events) as well as consequences of health-damaging behaviors (smoking, drinking, poor sleep and unhealthy diet) (Guidi et al., 2021; Thomson, 2019). When faced with environmental stressors, the organism must change the parameters of its internal physiological milieu and adapt them to achieve stability (Sterling, 1988). Once repeated or chronic environmental stressors exceed the organism's adaptive range, wear and tear on the body's systems occurs and allostatic load ensues (Seeman et al., 1997; Seeman et al., 2001). Allostatic load can be considered as a direct indicator of population frailty and has been found to be associated with all-cause mortality and multimorbidity. (Edes and Crews, 2017; Guidi et al., 2021; Juster et al., 2010; Seeman et al., 2001).

Emerging experimental evidence supports that the early initiating event elicited by pollutants inhalation is a stress response (Thomson, 2013; Thomson, 2019). Air pollutants act as chronic stressors and activate the neuroendocrine stress pathways, resulting in a wide range of physiologic responses in multiple organs (conceptualized as allostatic load) (Snow et al., 2018; Thomson, 2019), which is a common pathway implicated in various diseases (Guidi et al., 2021; Snow et al., 2018). Investigating the relationships between air pollution and allostatic load can therefore elucidate the mechanism linking air pollution to various diseases. However, few epidemiologic studies have examined the air pollution-allostatic load associations (Guidi et al., 2021; Jung et al., 2014; Montresor-López et al., 2021), especially in general populations with large sample sizes.

In this study, we examined the relationships between long-term exposure to ambient air pollutants (PM_1, $PM_{2.5}$, PM_{10}, and O_3) and allostatic load among nearly 90,000 Chinese adults aged 30–79 years. We used a doubly-robust causal modeling technique which can provide unbiased estimator in the case of either the propensity score model or the outcome model is specified correctly (Funk et al., 2011). In addition, since allostatic load is a combination of chemical/non-chemical stressors and intrinsic factors on body health (Guidi et al., 2021; Thomson, 2019), we further investigated the modification effect of intrinsic factors and other stressors on air pollution-induced allostatic load to identify vulnerable subpopulations. The study aimed at better understanding the role of air pollution as a chronic stressor in the common pathogenesis of various diseases.

2. Methods

2.1. Study design and participants

This cross-sectional study used baseline data from the China Multi-Ethnic Cohort (CMEC). Detailed design and implementation information of the CMEC has been reported previously (Zhao et al., 2021). In brief, CMEC recruited a total of 99,556 participants in five provinces of Southwest China (aged 30–79 years in Sichuan, Chongqing, Yunnan, Guizhou province; relaxing to 18–79 years in Tibet for shorter life expectancy) from May 2018 to September 2019. Using a multistage, stratified cluster sampling method, this cohort is aimed at being representative of the general populations in Southwest China. The baseline survey consisted of electronic questionnaires with face-to-face interviews, physical examinations, and clinical laboratory tests. The electronic questionnaire investigated demographic and socioeconomic information, disease history, family history, health behavior information, reproductive history, physical activity, dietary habits, and psychological status. The medical examination collected height, weight, blood pressure, heart rate, ultrasound, X-rays, vision screening, waist circumference, hip circumference, lung function, bone mineral density, and electrocardiogram. Clinical laboratory tests include routine blood tests, fasting blood glucose, blood lipids, liver function, and routine urine tests. All participants signed an informed consent form before conducting the investigation. Ethical approval was obtained from the Medical Ethics Review Committee of Sichuan University (K2016038, K2020022).

The current study included all the CMEC participants except for 1) the residents aged <30 years, 2) the residents in Aba area because they lived nomadically and had no fixed residence, 3) those with incomplete information on address, 4) those without complete clinical laboratory tests, and 5) those who had no available information on any adjusted covariates. After these exclusions, 85,545 participants aged 30–79 years on the day of the investigation were included in the following analyses (Supplementary Fig. S1).

2.2. Air pollution exposure assessment

The daily average concentrations of PM_1, $PM_{2.5}$, PM_{10} at a 1-km spatial resolution and O_3 at a 25-km resolution were predicted by space-time extremely randomized trees models using the Moderate Resolution Imaging Spectroradiometer Multiangle Implementation of Atmospheric Correction AOD product (for PM), pollution emissions, meteorology, land use information, and other spatial and temporal predictors. The previous studies have

reported a detailed description of the data collection and modeling process (Wei et al., 2019a; Wei et al., 2019b; Wei et al., 2020; Wei et al., 2021a; Wei et al., 2021b). These models were validated with 10-fold cross-validation R^2 (root mean square error) values for the daily predictions of PM_1, $PM_{2.5}$, PM_{10} and O_3 being 0.77 (14.6 μg/m^3), 0.90 (10.01 μg/m^3), 0.86 (24.28 μg/m^3), and 0.84 (20.11 μg/m^3), respectively. According to the geocoded residential addresses, the previous three-year average exposure concentrations of PM_1, $PM_{2.5}$, PM_{10}, and O_3 before the baseline survey were calculated for each participant as the substitute for long-term air pollution exposure.

2.3. Measurement of allostatic load index

Allostatic load is typically quantified using a multi-system framework, including a series of biomarkers that reflect physiological derangements. The choice of biomarkers for the construction of the allostatic load index was based on (i) representation of various physiological systems including cardiovascular, metabolic, anthropometric, and inflammatory parameters, (ii) prior allostatic load research (Barry et al., 2020; Egorov et al., 2020; Juster et al., 2010; Montresor-López et al., 2021; Ribeiro et al., 2019; Seeman et al., 1997; Seeman et al., 2001), and (iii) available CMEC measurements. Twelve biomarkers were selected to create a summary index representing allostatic load. Cardiovascular biomarkers included systolic blood pressure (SBP) and diastolic blood pressure (DBP). Metabolic biomarkers included triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDLC), total cholesterol (TC), fasting glucose, glycated hemoglobin (HbA1c), and creatinine clearance. Anthropometric markers were body mass index (BMI) and waist circumference (WC). The inflammatory biomarker was leukocyte. Detailed information about the measurement of biomarkers is as follows: At baseline survey, participants received a physical examination by trained personnel, including fasting weight, height, waist circumference, and fasting blood pressure. The BMI was calculated as the body weight (kg) divided by the height squared (m^2). The blood pressure (BP) measurements were performed three times in a seated, upright position. Participants were instructed not to smoke, drink alcohol, coffee, or tea, or exercise for at least 30 min prior to the measurement. The three measurements were averaged to calculate diastolic and systolic BP. All participants were collected with blood and urine samples at the collection sites. After overnight fasting (at least 8 h), venous blood samples were collected for clinical laboratory testing, including blood routine, fast blood glucose, lipid levels, and hepatic function, etc. Creatinine clearance (CCr) was calculated by the Cockcroft-Gault formula, where $CCr(\text{mL/min}) = [(140 - \text{age(years)}) * \text{weight (kg)}]/(0.818 * \text{serum creatinine (μmol/L)}$, corrected in women by a factor of 0.85.

The allostatic load index was defined as the sum of the sex-specific scores of the twelve biomarkers. For each of the biomarkers, the highest quartile in the population distribution by sex was considered 'high risk' and received a score of 1, except for HDL-C and creatinine clearance, where the lowest quartile was considered 'high risk'(Barrett et al., 2018; Berger et al., 2018; Robertson et al., 2015). Allostatic load biomarkers and the respective cut-off values are presented in Table 1. Then, we totaled all the biomarker scores to obtain an allostatic load index ranging from 0 to 12 for each participant. Higher scores of the allostatic load index imply greater physiological dysfunction.

2.4. Covariate assessment

We adjusted for covariates in both the propensity score model (design stage) and the outcome regression model (analysis stage). According to the recommendation of Austin et al., two types covariates were examined (Austin et al., 2007): the potential confounders of ambient air pollution-allostatic load and the risk/protective factors related to allostatic load. Referring to previous literature has reported: i) potential confounders included region and residential greenness (Egorov et al., 2017, 2020; Ribeiro et al., 2019); ii) factors related to allostatic load included demographics (age at the baseline survey, sex, and ethnicity) (Kusano et al., 2016; Langellier et al., 2021; Shiels et al., 2019), socioeconomic factors (education level and annual family income) (Howard and Sparks, 2015; Johnson et al., 2017; Upchurch et al., 2015), lifestyle risk factors (smoking status, alcohol drinking status, and physical activity) (Petrovic et al., 2016; Robinette et al., 2016), diet (fruits, vegetable, and red meat intake) (Mattei et al., 2013; Suvarna et al., 2020), and environmental variable (secondary smoking and indoor air pollution) (Jung et al., 2014; Robinette et al., 2016). The covariate definitions are shown in Supplementary Table S1.

Table 1
Allostatic load biomarkers and the respective cut-off values.

Biomarker	Unit	Mean (SD)	Cut-off value	
			Male	Female
Cardiovascular				
SBP	mm Hg	126.44 (19.62)	139.67	136.00
DBP	mm Hg	79.56 (11.42)	89.00	84.30
Metabolic				
Triglycerides	mmol/L	1.72 (1.59)	2.20	1.81
LDL-C	mmol/L	2.93 (0.84)	3.46	3.41
HDL-C	mmol/L	1.48 (0.40)	1.11	1.28
TC	mmol/L	5.01 (1.01)	5.60	5.59
fasting glucose	mmol/L	5.41 (1.42)	5.70	5.51
HbA1c	%	5.75 (0.92)	6.00	5.90
Creatinine clearance	mL/min	88.73 (25.92)	71.55	70.14
Inflammatory				
leukocyte	10^9/L	6.15 (1.69)	7.30	6.90
Anthropometric				
BMI	kg/m^2	24.11 (3.41)	26.49	26.12
waist circumference	cm	82.35 (10.11)	92.00	87.00

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycosylated hemoglobin; BMI, Body mass index.

2.5. Statistical analysis

In the present study, we applied a doubly-robust approach, which has been efficiently used for analyzing the associations between air pollution and various health outcomes in several previous papers (M. D. Yazdi et al., 2021a; M. D. Yazdi et al., 2021b). For each exposure, the analysis consisted of 2 stages: 1) a design stage where the generalized propensity scores (GPS) and corresponding inverse-probability weights (IPWs) were estimated using the linear model to construct a pseudo population in which covariates were balanced across exposure levels, and 2) an analysis stage where the Poisson regression model was run to estimate the allostatic load given the covariates and exposures in the pseudo population. The implementation of the doubly-robust approach was described in Supplementary S1. Since a Poisson regression model was used as the outcome model, results are presented as the relative risk (RR) of allostatic load associated with a 10 μg/m^3 increase in specific air pollution concentrations. In terms of the uncertainty during the design stage of GPS calculating, the standard errors of coefficients were re-estimated in a sandwich method (Zhang et al., 2016). The balance of covariates (after weighting) was also assessed by calculating the average absolute correlations between the exposures and the covariates (Supplementary Fig. S2) (Zhu et al., 2015).

We also evaluated the effect modification by individual factors and other non-chemical stressors, including age, sex, ethnicity, education level, family income level, smoking status, alcohol drinking status, and physical activity. Each potential effect modification was assessed by adding multiplicative interaction terms between air pollution and the modifier to be evaluated. To test the statistical significance of the effect modification, we evaluated the heterogeneity among different strata.

2.6. Sensitivity analyses

To assess the robustness of our findings, we performed a series of sensitivity analyses by 1) additionally adjusting for psychological factors

(anxiety, depression, insomnia, and major life events occurring); 2) excluding participants from Tibet, where the environment is quite distinguished from other regions (the unique environment in Tibet is high altitude with generally >3500 m above sea level, low atmospheric pressure, hypoxia, and extreme cold); 3) excluding participants who resided at their present address for fewer than three years; 4) excluding participants with self-reported diabetes, hypertension, hyperlipidemia, cardiovascular diseases, malignant tumors, tuberculosis, cirrhosis, and pregnancy.

In addition, we used the cubic spline transformation of air pollution to investigate the linearity. The average concentrations of air pollution for one, two, and four years before the baseline survey were used to evaluate the influence of the exposure windows. Two types of air pollutants (particulate matter including PM_1, $PM_{2.5}$, and PM_{10}, and a gaseous air pollutant O_3) were included in the analyses. We also implemented a paired pollution model for each pollutant by adjusting another type of pollutant. We calculated Evidence-for-causality values (*E*-values) for our main results. E-value is the minimum strength of an unmeasured confounder which must be related to both exposure and outcome to explain away a study result, conditional on all measured covariates (VanderWeele and Ding, 2017). A high *E*-value indicates that considerable strongly unmeasured confounding would be needed to distort a study result. For an observed RR, E-value is calculated as follows: $E - value = RR + sqrt\{RR * (RR - 1)\}$ (Ding and VanderWeele, 2016, VanderWeele and Ding, 2017). Finally, we re-examined the main analyses between air pollution and allostatic load by the traditional regression approach.

All statistical analyses were conducted in R version 4.1.0.

3. Results

3.1. Descriptive characteristics and air pollutant concentrations

The baseline characteristics of the study participants are presented in Table 2 and Supplementary Table S2. A total of 85,545 participants were included in the main analyses. The mean age of the participants was 51.65 years (SD: 11.47). Approximately 60% of the participants were female, and 39% were the minority. The mean allostatic load score was 3.06 (SD: 2.26). Compared to people with low $PM_{2.5}$ exposure, people with high $PM_{2.5}$ exposure were more likely to smoke and drink alcohol, had higher education and income, and had lower physical activity. While compared to those with low O_3 exposure, those with high O_3 exposure had lower education and income and higher physical activity level.

The distribution of the air pollution concentrations for each participant is displayed in Fig. 1, Supplementary Table S3 and Fig. S4. The medians of air pollution exposure levels were 27.8 μg/m^3 (range: 6.1–53.6), 37.7 μg/m^3 (range: 11.8–105.3), 65.8 μg/m^3 (range: 33.1–165.2), and 80.1 μg/m^3 (range: 56.2–95.4) for PM_1, $PM_{2.5}$, PM_{10}, and O_3, respectively.

3.2. Associations between outdoor air pollution and allostatic load

The associations between long-term exposure to air pollution and allostatic load are presented in Table 3. Increased $PM_{2.5}$, PM_{10}, and O_3 were significantly associated with increased allostatic load. Every 10 μg/m^3 increase in the three-year average $PM_{2.5}$, PM_{10}, and O_3 concentrations, the *RR* (*95%CI*) of allostatic load was 1.040 (1.024, 1.057), 1.029 (1.018, 1.039) and 1.087 (1.074, 1.101), respectively. The *E*-value was 1.16, 1.24, 1.20, 1.39 for PM_1, $PM_{2.5}$, PM_{10}, O_3, respectively. Take $PM_{2.5}$ for example, the E-value of 1.24 implied that the observed *RR* of 1.04 could be explained away by an unmeasured confounder that was related to both ambient $PM_{2.5}$ and allostatic load by a RR of 1.24 -fold each, above and beyond the measured confounders, but weaker confounding could not do so. The likelihood of containing such strength of unmeasured confounder to distort the study result was relatively low because an adjustment has been made for a sufficient number of confounding variables.

3.3. Modification analyses

Evidence of effect modification by individual factors and other potential stressors is displayed in Fig. 2 (and Supplementary Table S5). The associations between PM and allostatic load were modified by age, ethnicity, education level, income level, and alcohol drinking status. The associations between PM and allostatic load were significantly increased among participants with older, minority, lower education and lower-income group, and regularly drinking. For example, the *RR* (*95% CI*) of allostatic load for each 10 μg/m^3 increase in $PM_{2.5}$ was 1.043 (1.025, 1.062) for people older than 60 years, 1.176 (1.139, 1.215) for minority, 1.049 (1.031, 1.067) for the primary school or below group, 1.049 (1.032, 1.067) for people whose annual family income was less than 20, 000 yuan, and 1.061 (1.042, 1.079) for people who regularly drink. For O_3, the results suggested that ethnicity, education level, income level, and physical activity could modify the O_3-allostatic load associations. We found the relationships between O_3 and allostatic load were significantly increased among participants with minority, lower education, lower-income level, and higher physical activities.

3.4. Sensitivity analyses

The estimated RRs of allostatic load for air pollution exposure were similar when additionally adjusting for mental health-related factors (Table 4). We also observed similar results when sequentially excluding participants with those living in Tibet, those at the current residence less than three years, those who are chronically ill or pregnant (Table 4).

The exposure-response relationships between air pollution and allostatic load were approximately linear (Supplementary Fig. S3). We observed that the associations between air pollution and allostatic load remained robust when using average air pollution concentrations for a series of exposure windows (Table 5). The association of each pollutant with allostatic load also remained generally consistent after the inclusion of another pollutant, indicating the independent effect of each other (Fig. 3 and Supplementary Table S4). Lastly, all of the results were almost consistent after using the traditional regression approach, except that the uncertainty of the estimated effect was slightly smaller than that of using the causal doubly-robust approach (Supplementary S3).

4. Discussion

Using a large-scale cohort of nearly 90,000 adults aged 30–79 years enrolled in Southwest China, we found that long-term exposure to PM ($PM_{2.5}$ and PM_{10}) and O_3 was associated with an increased risk of allostatic load. The associations between air pollution and allostatic load were consistent even after a series of sensitivity analyses and two kinds of analysis strategies (causal doubly-robust and traditional regression approaches). Factors such as age, ethnicity, and socioeconomic status generally modified these relationships, as the elderly, minority, lower educated, and lower-income had significantly higher air pollution-related allostatic load. To our knowledge, the current study is the first and largest epidemiologic study to investigate the associations between long-term exposure to ambient air pollution and the allostatic load among the general population.

4.1. Biological mechanism and experimental evidence

The potential mechanisms underlying the relationships between air pollution and allostatic load are linked to the neuroendocrine response system (Snow et al., 2018; Thomson, 2019). The neuroendocrine response is activated when inhaling air pollution, leading to a wide range of physiological responses. If this process occurs repeatedly and chronically, allostatic load ensues. Specifically, air pollution inhalation triggers sensory signals and pulmonary mediators that travel to the brain and then may lead to neuroendocrine stress responses, including activating the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes (Snow et al., 2018; Thomson, 2013; Thomson, 2019). Activation of the HPA axis and SAM axis releases stress hormones (such as epinephrine,

Table 2
Characteristics of the study participants by low and high $PM_{2.5}/O_3$ exposure.

Variables	Overall	$PM_{2.5}$ (μg/m^3)[a]		O_3 (μg/m^3)[a]	
		Low (11.8–37.7)	High (37.7–105.0)	Low (56.2–80.1)	High (80.1–95.4)
Population	85,545	42,836	42,709	43,378	42,167
Age (SD)	51.65 (11.47)	52.23 (10.89)	51.08 (12.00)	51.64 (11.50)	51.67 (11.43)
Sex (%)					
Male	33,878 (39.6)	14,654 (34.2)	19,224 (45.0)	17,700 (40.8)	16,178 (38.4)
Female	51,667 (60.4)	28,182 (65.8)	23,485 (55.0)	25,678 (59.2)	25,989 (61.6)
Ethnicity (%)					
Han	52,176 (61.0)	107,73 (25.1)	41,403 (96.9)	26,422 (60.9)	25,754 (61.1)
Minority[b]	33,369 (39.0)	32,063 (74.9)	1306 (3.1)	16,956 (39.1)	16,413 (38.9)
Education level (%)					
Illiteracy	20,700 (24.2)	15,990 (37.3)	4710 (11.0)	10,191 (23.5)	10,509 (24.9)
Primary school	21,963 (25.7)	12,825 (29.9)	9138 (21.4)	9370 (21.6)	12,593 (29.9)
Junior high school	22,794 (26.6)	9148 (21.4)	13,646 (32.0)	12,036 (27.7)	10,758 (25.5)
High school	10,329 (12.1)	2642 (6.2)	7687 (18.0)	6096 (14.1)	4233 (10.0)
Junior college and above	9759 (11.4)	2231 (5.2)	7528 (17.6)	5685 (13.1)	4074 (9.7)
Annual family income, yuan (%)					
<12,000	14,841 (17.3)	10,263 (24.0)	4578 (10.7)	7702 (17.8)	7139 (16.9)
12,000–19,999	15,033 (17.6)	9710 (22.7)	5323 (12.5)	6891 (15.9)	8142 (19.3)
20,000–59,999	30,763 (36.0)	15,626 (36.5)	15,137 (35.4)	14,705 (33.9)	16,058 (38.1)
60,000–99,999	12,969 (15.2)	4065 (9.5)	8904 (20.8)	7389 (17.0)	5580 (13.2)
≥100,000	11,939 (14.0)	3172 (7.4)	8767 (20.5)	6691 (15.4)	5248 (12.4)
Smoking status (%)					
Never smoking	63,508 (74.2)	33,173 (77.4)	30,335 (71.0)	32,700 (75.4)	30,808 (73.1)
Quit smoking	4331 (5.1)	1561 (3.6)	2770 (6.5)	2284 (5.3)	2047 (4.9)
Smoking	17,706 (20.7)	8102 (18.9)	9604 (22.5)	8394 (19.4)	9312 (22.1)
Alcohol drinking status (%)					
Never	47,697 (55.8)	27,663 (64.6)	20,034 (46.9)	21,287 (49.1)	26,410 (62.6)
Occasionally	26,355 (30.8)	10,508 (24.5)	15,847 (37.1)	16,203 (37.4)	10,152 (24.1)
Regularly	11,493 (13.4)	4665 (10.9)	6828 (16.0)	5888 (13.6)	5605 (13.3)
Secondary smoking (%)					
Yes	42,964 (50.2)	20,973 (49.0)	21,991 (51.5)	22,448 (51.7)	20,516 (48.7)
No	42,581 (49.8)	21,863 (51.0)	20,718 (48.5)	20,930 (48.3)	21,651 (51.3)
Indoor air pollution (%)					
Low	13,449 (15.7)	6368 (14.9)	7081 (16.6)	6947 (16.0)	6502 (15.4)
Moderate	67,851 (79.3)	33,161 (77.4)	34,690 (81.2)	34,228 (78.9)	33,623 (79.7)
High	4245 (5.0)	3307 (7.7)	938 (2.2)	2203 (5.1)	2042 (4.8)
Fruits intake (%)					
Never or little	15,145 (17.7)	8707 (20.3)	6438 (15.1)	9105 (21.0)	6040 (14.3)
1–3 day/week	21,802 (25.5)	11,260 (26.3)	10,542 (24.7)	11,104 (25.6)	10,698 (25.4)
4–6 day/week	3419 (4.0)	1538 (3.6)	1881 (4.4)	1985 (4.6)	1434 (3.4)
Every day	45,179 (52.8)	21,331 (49.8)	23,848 (55.8)	21,184 (48.8)	23,995 (56.9)
Vegetable intake (%)					
Never or little	587 (0.7)	386 (0.9)	201 (0.5)	254 (0.6)	333 (0.8)
1–3 day/week	1107 (1.3)	739 (1.7)	368 (0.9)	382 (0.9)	725 (1.7)
4–6 day/week	298 (0.3)	193 (0.5)	105 (0.2)	117 (0.3)	181 (0.4)
Every day	83,553 (97.7)	41,518 (96.9)	42,035 (98.4)	42,625 (98.3)	40,928 (97.1)
Red meat intake (%)					
Never or little	8253 (9.6)	6030 (14.1)	2223 (5.2)	3262 (7.5)	4991 (11.8)
1–3 day/week	13,978 (16.3)	7770 (18.1)	6208 (14.5)	6058 (14.0)	7920 (18.8)
4–6 day/week	2402 (2.8)	1063 (2.5)	1339 (3.1)	1256 (2.9)	1146 (2.7)
Every day	60,912 (71.2)	27,973 (65.3)	32,939 (77.1)	32,802 (75.6)	28,110 (66.7)
Physical activity, METs/d (%)					
Quintile 1 [0,11.7]	20,633 (24.1)	8768 (20.5)	11,865 (27.8)	10,198 (23.5)	10,435 (24.7)
Quintile 2 (11.7,21.9]	21,389 (25.0)	8447 (19.7)	12,942 (30.3)	11,063 (25.5)	10,326 (24.5)
Quintile 3 (21.9,37.2]	21,752 (25.4)	11,220 (26.2)	10,532 (24.7)	11,502 (26.5)	10,250 (24.3)
Quintile 4 (37.2142]	21,771 (25.4)	14,401 (33.6)	7370 (17.3)	10,615 (24.5)	11,156 (26.5)
Residential greenness, NDVI (mean (SD))	0.39 (0.13)	0.44 (0.12)	0.35 (0.12)	0.40 (0.13)	0.38 (0.12)
Allostatic load index (mean (SD))	3.06 (2.26)	3.27 (2.24)	2.85 (2.26)	2.94 (2.28)	3.18 (2.23)

Data are the mean (standard deviation, SD) for continuous variables and number (percentage) for categorical variables.
Abbreviations: METs, metabolic equivalent tasks; NDVI, the Normalized Difference Vegetation Index.
[a] The cut-off value for air pollution concentrations is based on the median, where less than or equal to the median is defined as low concentration.
[b] Minority includes Buyi ethnicity, Dong ethnicity, Miao ethnicity, Bai ethnicity, Yi ethnicity and Tibetan.

norepinephrine, and glucocorticoids) from the adrenal gland into the circulation (Koren et al., 2012; Ranabir and Reetu, 2011). In addition, sympathetic nerve endings distributed throughout all organs produce norepinephrine locally. These stress hormones can mediate a wide range of physiological effects through activating adrenergic and glucocorticoid receptors, such as lipid synthesis and redistribution, insulin secretion,

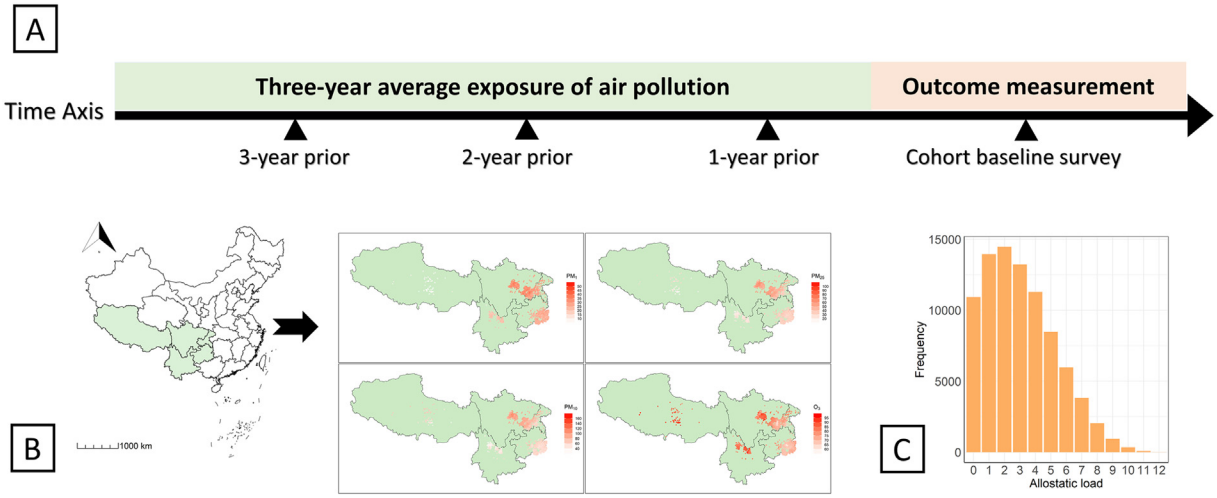

Fig. 1. Study design and the distributions of exposure and outcome. A is the study design, including the measurement time of exposure and outcome. B is the maps of the three-year average air pollution exposure for the study participants (The separate exposure map is shown in Fig. S4). C is the distribution of allostatic load scores among study participants.

inflammation, vasoconstriction, and so on (Thomson, 2013). The neuroendocrine system is critical for normal homeostasis (Ramsay and Woods, 2014). If exposed to air pollution for a long time, the persistent activation in the neuroendocrine response system can break the allostasis balance and result in allostatic load (Snow et al., 2018; Thomson, 2019). The damage during these processes can eventually lead to cardiometabolic disease, neurodegenerative disease and developmental abnormalities (Juster et al., 2010; Snow et al., 2018).

Multiple experimental studies have provided evidence to support the mechanisms above mentioned. In an animal study, rats' exposure to concentrated air particles activated the stress axis and increased the corticosterone level compared to rats' exposure to normal air (Sirivelu et al., 2006). Thomson et al. mapped gene expression profiles across various tissues in Fischer rats exposed to PM or O_3 (relative to air-exposed controls) and found that exposure to pollutants can activate the HPA axis and produce common systemic effects (Thomson et al., 2013). A recent animal study showed that the adrenergic and glucocorticoid receptor antagonists can reduce pulmonary injury and inflammatory effects caused by O_3 (Henriquez et al., 2018). In a randomized, double-blind crossover trial of 55 students, using air purifiers to reduce indoor PM was associated with reductions in the stress hormone, suggesting that higher PM may activate the HPA and SAM axes, and then induce metabolic alterations (Li et al., 2017). Another randomized, double-blind, crossover trial of 22 healthy young adults found that acute ozone exposure increased the secretion of neuroendocrine stress hormones (Wang et al., 2022).

Table 3
Relative risk (RR, *95% CI*) of allostatic load associated with each 10 μg/m^3 increase in three-year average concentrations of PM_1, $PM_{2.5}$, PM_{10}, and O_3.

Air pollution	Relative risk (RR)[b]	95% CI	E value[a]
PM_1	1.020	(0.990, 1.050)	1.16 (1.00)
$PM_{2.5}$	1.040	(1.024, 1.057)	1.24 (1.18)
PM_{10}	1.029	(1.018, 1.039)	1.20 (1.15)
O_3	1.087	(1.074, 1.101)	1.39 (1.36)

Abbreviations: PM_1, particles with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$; particles with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particles with aerodynamic diameter ≤ 10 μm; O_3, ozone.

[a] *E*-value for point estimates and the lower bound of the 95% confidence of the relative risk.

[b] Adjusted for age, sex, ethnicity, region, education level, annual family income, smoking status, alcohol drinking status, physical activity, fruits intake, vegetable intake, red meat intake, secondary smoking, indoor air pollution, and residential greenness.

4.2. Comparison with other studies

Only two relevant epidemiologic studies examined the effect of air pollution on allostatic load. One cross-sectional study among 115 office workers in Taiwan examined the relationship of indoor environmental quality with allostatic load score (Jung et al., 2014). The result reported no significant association between indoor $PM_{2.5}$ exposure and total allostatic load score. Another cross-sectional study of 2338 youth with type 1 diabetes investigated the effects of long-term exposures to traffic-related air pollutants on allostatic load (Montresor-López et al., 2021). This study still reported no significant associations in the main analysis, while a higher allostatic load was observed for non-white participants who lived closer to heavily-trafficked roads in stratified analyses. The insignificant associations between PM and allostatic load found in these two studies may due to the relatively small sample sizes to some extent. Collectively, the current study is the first to find significant positive correlations between long-term exposure to PM and O_3 and allostatic load in a large general population. Moreover, *E*-value analysis were performed to quantify the strength of the observed association against potential unmeasured confounders, which may help to improve the ability of researches to assess evidence from the observational study (VanderWeele and Ding, 2017).

4.3. Modification effect

In this study, we observed that the elderly and minorities might suffer greater harmful effects of air pollution on allostatic load than younger and Han. Studies have shown that physiological challenges, represented by allostatic load, increase with age (Crimmins et al., 2003). The modification effect of age on air pollution-induced allostatic load may be due to brain structural changes (Ritchie et al., 2017), white matter and brain volume decreasing (Booth et al., 2015), and physiological decline in the elderly (Crimmins et al., 2003). Furthermore, despite improvements in living standards and conditions in less-developed ethnic minority regions, certain economic and health disparities still exist. Some of ethnic minorities are concentrated in remote rural regions, while a larger proportion of Han resides in urban areas. The inequality in socioeconomic status levels between urban and remote rural areas may be a possible explanation for the worse health effect among minorities. Rural inhabitants have lower income, education, and quality of health services, probably leading to less awareness of proactive health care compared with urban residents (Chen et al., 2019; Chen et al., 2020). Our results suggest that the elderly and minorities would be better to take more protection against air pollution exposure and to be allocated more health resources.

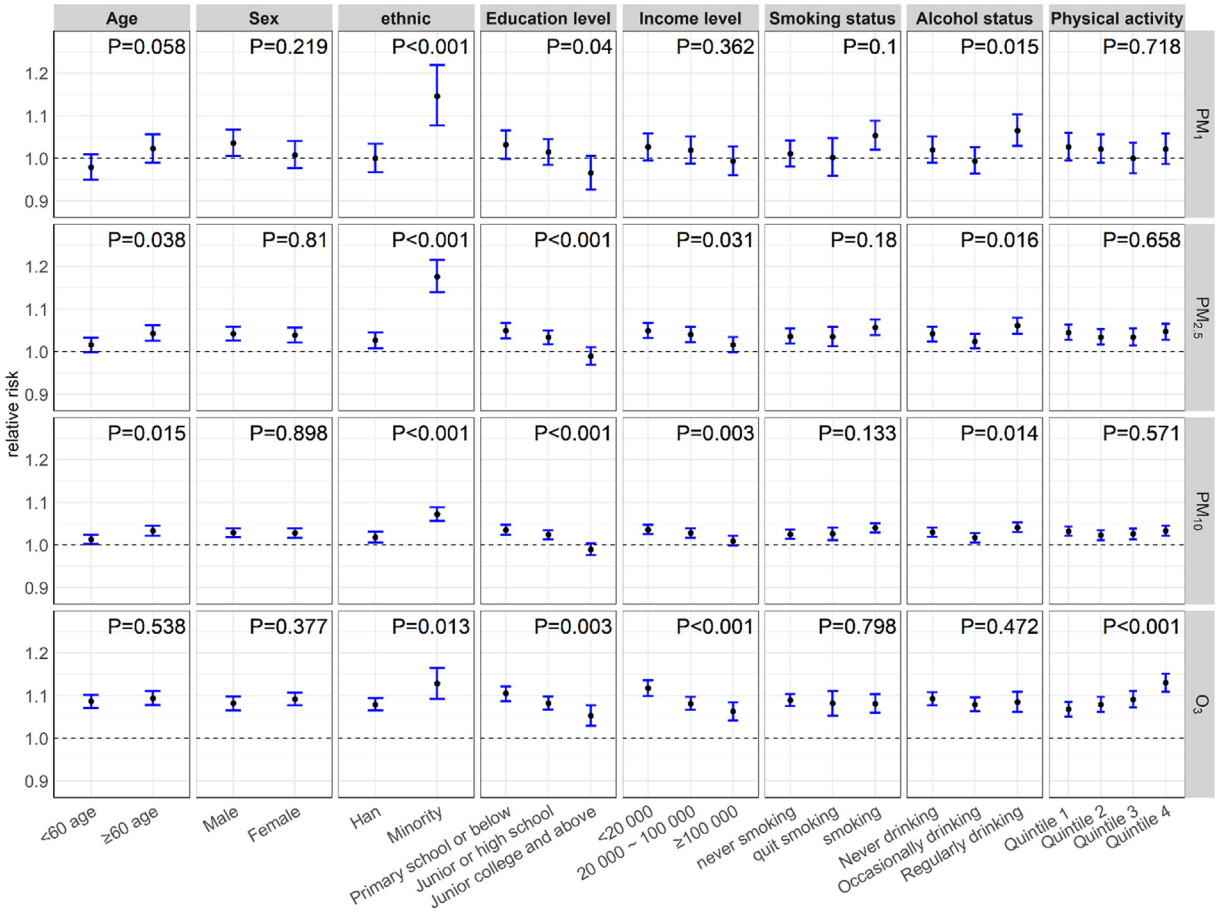

Fig. 2. Relative risks (*95% CI*) of allostatic load associated with each 10 μg/m^3 increase in three-year average concentrations of PM_1, $PM_{2.5}$, PM_{10}, and O_3, modified by individual factors and some other non-chemical stressors. The effects were estimated after adjusting for age, sex, ethnicity, region, education level, annual family income, smoking status, alcohol drinking status, physical activity, fruits intake, vegetable intake, red meat intake, secondary smoking, indoor air pollution, and residential greenness (excluding the evaluated effect modifier). Statistically significant modifier effects were tested using a heterogeneity test. Abbreviations: PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; O_3, ozone.

In addition to the intrinsic factors (age and ethnicity), the current study highlights that socioeconomic position (education and income level) might modify the associations between air pollution and allostatic load. This finding is consistent with the evidence from previous studies indicating that lower education and income, acting as a chronic stressor, is a risk factor for allostatic load (Dowd et al., 2009; Gustafsson et al., 2011; Hawkley et al., 2011; Hickson et al., 2012; Robertson et al., 2015). Previous studies have also reported that simultaneous exposure to non-chemical stressors exacerbates the effects of air pollutants on allostatic load (Clougherty et al., 2007; Hicken et al., 2014; Shankardass et al., 2009). Interestingly, we found the association between O_3 and allostatic load was significantly increased among participants with higher physical activities. The reason may be related to adipose lipolysis. A crossover clinical study found exposure to O_3 alongside exercise increases circulating free fatty acids and glycerol (Miller et al., 2016). Moreover, areas with higher physical activity include more field workers or migrant workers who spend a lot of time

Table 4
Sensitivity analyses for the association of allostatic load with each 10 μg/m^3 increase in three-year average concentrations of PM_1, $PM_{2.5}$, PM_{10}, and O_3.

	PM_1	$PM_{2.5}$	PM_{10}	O_3
Main analyses[a]	1.020 (0.990, 1.050)	1.040 (1.024, 1.057)	1.029 (1.018, 1.039)	1.087 (1.074, 1.101)
Additional adjustment for:				
Mental health-related factors[b]	1.022 (0.997, 1.048)	1.033 (1.019, 1.047)	1.028 (1.019, 1.036)	1.063 (1.051, 1.075)
Additional excluding:				
Those living in Tibet	1.031 (1.001, 1.062)	1.039 (1.023, 1.056)	1.029 (1.018, 1.040)	1.089 (1.075, 1.102)
Those at the current residence <3 years	1.034 (1.002, 1.068)	1.040 (1.023, 1.058)	1.029 (1.018, 1.041)	1.090 (1.076, 1.104)
Those with specific diseases[c]	1.021 (0.986, 1.058)	1.032 (1.014, 1.051)	1.021 (1.009, 1.033)	1.085 (1.068, 1.101)

Abbreviation: PM_1, particles with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$; particles with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particles with aerodynamic diameter ≤ 10 μm; O_3, ozone.

[a] Main analyses: adjusted for age, sex, ethnicity, region, education level, annual family income, smoking status, alcohol drinking status, physical activity, fruits intake, vegetable intake, red meat intake, secondary smoking, indoor air pollution and residential greenness.

[b] mental health-related factors included: anxiety, depression, insomnia, and major life events.

[c] specific diseases included: diabetes, hypertension, hyperlipidemia, cardiovascular diseases, malignant tumors, tuberculosis, cirrhosis or pregnancy.

Table 5
Relative risks (RR, *95% CI*) of allostatic load associated with air pollution by different exposure windows.

Air pollution	Exposure windows[a]			
	One year	Two years	Three years	Four years
PM_1	1.011 (0.989, 1.033)	1.032 (1.004, 1.061)	1.020 (0.990, 1.050)	1.021 (0.993, 1.049)
$PM_{2.5}$	1.033 (1.017, 1.049)	1.037 (1.021, 1.054)	1.040 (1.024, 1.057)	1.043 (1.026, 1.060)
PM_{10}	1.028 (1.019, 1.038)	1.032 (1.022, 1.041)	1.029 (1.018, 1.039)	1.029 (1.018, 1.039)
O_3	1.091 (1.076, 1.106)	1.060 (1.046, 1.075)	1.087 (1.074, 1.101)	1.081 (1.068, 1.095)

Abbreviation: PM_1, particles with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$; particles with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particles with aerodynamic diameter ≤ 10 μm; O_3, ozone.
[a] Adjusted for age, sex, ethnicity, region, education level, annual family income, smoking status, alcohol drinking status, physical activity, fruits intake, vegetable intake, red meat intake, secondary smoking, indoor air pollution and residential greenness.

outdoors and may have poorer health condition despite having higher physical activity than the average person. In addition to air pollutants, other environmental, social, and individual stressors, as well as the resulting health-damaging behaviors may play together to affect allostatic loads. Research on the combined and cumulative effects of air pollution and multiple other stressors and the characteristics of their interactions may be important. Future research will provide insight into such issues.

4.4. Limitations and strengths

The current study has some limitations. First, primary mediators, comprising stress-related hormones (such as cortisol) in response to acute stressors, were not included in the allostatic load score because of data unavailability in the CMEC. Indeed, our study included secondary mediators resulting from the long-term actions of the primary mediators as much as possible. The current study examined the effect of long-term exposure to air pollution, and it seems reasonable to construct allostatic load scores using secondary mediators. Second, we calculate the allostatic load score by assigning equal weights to twelve biomarkers, possibly ignoring the different contributions of biomarkers to allostatic load. Third, we used the traditional approach (75th or 25th percentile bounds by age) to define high-risk cut-offs for the AL biomarkers, which may not accurately represent the true clinical status. However, the theory of allostatic load focuses on measuring sub-clinical dysregulation, and thus the cut offs of distribution may be more appropriate than clinical reference values (Seplaki et al., 2005). Finally, we assessed participants' air pollution exposure levels at their residential address, which may not fully represent the actual exposure levels given their activity patterns.

Apart from the shortcomings mentioned, this study has some advantages. The study's participants were from the baseline survey of a large and well-characterized cohort, which incorporated extensive personal information, such as detailed lifestyle factors and indoor air pollution information. This helps us to adjust for confounders more fully. Lastly, this study used a doubly-robust causal approach mimicking randomized trials with a counterfactual framework. This approach will similarly produce an unbiased causal estimator either the inverse probability weighting model or the outcome model are correctly specified. After conducting several sensitivity analyses, the results were consistent and have not substantial changed.

5. Conclusion

This study identified that long-term exposure to ambient air pollution (PMs and O_3) was significantly associated with an increased risk of allostatic load. We also found that increasing age, minorities, lower education and lower income may exacerbate the harmful effects of air pollution. Our findings add the epidemiological evidence about the ambient pollutants' broad damaging effects on multiple organs and systems. Ambient air pollution acting as a chronic stressor leads to allostatic load, which may be the linkage of various air pollution-related diseases.

CRediT authorship contribution statement

Huan Xu and Tingting Yang analyzed the data, drafted the article and contributed to investigation and data collection in CMEC. Bing Guo, Yangzong Silang, Yingxue Dai, Kangzhuo Baima, Yang Gao, and Simei Tang contributed to investigation and data collection in CMEC. Jing Wei provided exposure data and contributed to discussion. Bing Guo, Ye Jiang, Shiyu Feng and Sicheng Li contributed to result visualization and discussion. Xiong Xiao provided conception and design of the study, as well as edited the article and contributed to discussion. Xing Zhao contributed to

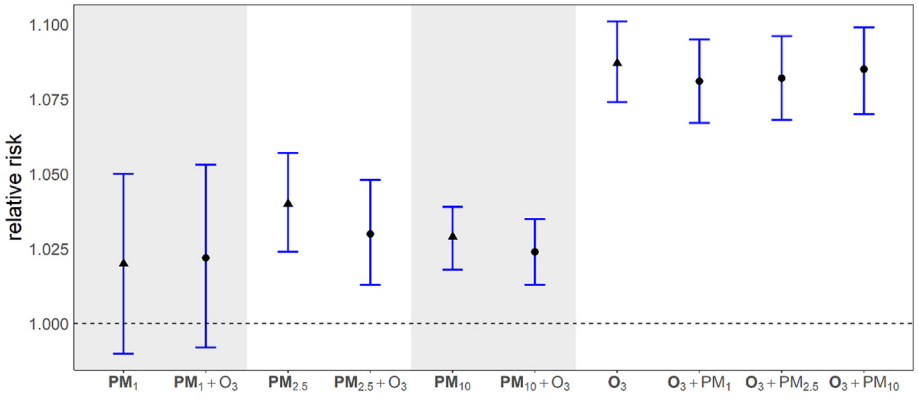

Fig. 3. Associations between ambient air pollutants and allostatic load in single pollutant models and two-pollutant models. Abbreviations: PM_1, particles with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$; particles with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particles with aerodynamic diameter ≤ 10 μm; O_3, ozone. Note: Bold character indicated the pollutant effect presented in the figure; Triangle, the relative risk of allostatic load in the single-pollutant models; Circles, the relative risk of allostatic load in the two-pollutant models.

the overall design and supervised the conduct of the CMEC study. All authors revised the article critically.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155658.

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