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Joint exposure to air pollution, ambient temperature and residential greenness and their association with metabolic syndrome (MetS): A large population-based study among Chinese adults

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ABSTRACT

Previous studies assessing adverse health have traditionally focused on a single environmental exposure, failing to reflect the reality of various exposures present simultaneously. Air pollution, ambient temperature and greenness have been proposed as critical environmental factors associated with metabolic syndrome (MetS). However, evidence exploring their joint relationships with MetS is needed for identifying interactive factors and developing more targeted public health interventions. The baseline data was obtained from China Multi-Ethnic Cohort (CMEC). Environmental data of air pollutants ($PM_{2.5}$, O_3) and NDVI for greenness was calculated from satellites data. Ambient temperature data were obtained from European Center for Medium-Range Weather Forecasts (ECMWF). MetS was classified based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) using anthropometric measures and biomarkers. Logistic regression models were utilized to examine the combined relationship of MetS with three-year exposure to air pollutants, temperature and NDVI. Relative excess risk due to interaction (RERI) was calculated to evaluate interaction on an additive scale. We found associations between prevalent MetS and interquartile range (IQR) increases in $PM_{2.5}$ (OR: 1.38; 95% confidence interval [95% CI]: 1.23, 1.55) and O_3 (OR: 1.15; 95% CI: 1.09, 1.22). Additive and multiplicative interactions were observed between air pollutants and temperature exposure. Compared to low-temperature level, the relationship between $PM_{2.5}$ and MetS attenuated (RERI: 0.22, 95% CI: 0.44, −0.04) at high-temperature level, while the relationship between O_3 and MetS enhanced (RERI: 0.05, 95% CI: 0.02, 0.11). At low NDVI 250 m, the association between $PM_{2.5}$ and MetS was stronger (RERI: 0.13, 95% CI: 0.05, 0.19) with high NDVI 250 m as the reference group. Our findings showed that ambient temperature and residential greenness could affect the relationship between air pollutants and MetS.

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1. Introduction

Environmental exposure is an important health determinant (Prüs-s-Ustün et al., 2019). Approximately 90% of the population worldwide is under threats of polluted air, with particulate matter (PM) and ozone (O_3) consistently being of major concerns, especially in industrialized areas ("9 out of 10 people worldwide breathe polluted air, but more countries are taking action," n. d.; Wang et al., 2017). Over the past few decades, increased greenhouse gas emissions have led to faster global warming, with seven of 10 years of the highest annual temperatures occurring after 2014 ("More Near-Record Warm Years Are Likely On Horizon," 2020). As rapid urbanization progresses, greenness, which is generally thought to benefit health, is an important component of infrastructure development and urban planning (Fong et al., 2018; Zhao et al., 2013). Based on complex environmental conditions, several publications have assessed the deleterious or protective effects of diverse environmental factors on individual health but only considered each individually or adjusted for the exposure to other factors (Gu et al., 2020; Sun et al., 2010; Valdés et al., 2014; Wang et al., 2021).

Indeed, humans are exposed to a mixture of various environmental factors acting synergistically or antagonistically with one another (Gibson et al., 2019; Kinney, 2018). The scientific community and policymakers have recommended shifting to a multi-exposure approach to better protect the public from the effects of environmental factors as a whole (Dominici et al., 2010). The principal motivation is to fully characterize the complexity of the exposure and their health impacts through identifying interactions arising from combined exposures. In addition, the multi-exposure approach allows to inform maximally efficient targeted interventions and regulations.

Metabolic syndrome (MetS) is composed of an assembly of metabolic risk factors accompanied by an increasing risk of cardiovascular disease (CVD) and type 2 diabetes (Alberti et al., 2009). Metabolic syndrome-related diseases (MSRD) and related complications, especially atherosclerotic cardiovascular disease, constitute a major disease burden in both developed and developing countries (Grundy et al., 2005; Murray et al., 2020). With an estimated prevalence of approximately 20–30% of adults worldwide in 2015, MetS has become an urgent global health problem (O'Neill and O'Driscoll, 2015).

Current research has proposed air pollution, ambient temperature and green space as potential environmental risk or protective factors for MetS (de Keijzer et al., 2019; Wallwork et al., 2017; Yang et al., 2020; Yu et al., 2020). However, the importance of assessing multiple environmental exposures jointly has been increasingly recognized. Whereas some studies have proposed that ambient temperature change could lead to physiological stress and alter the response to toxic pollutants of tissues and organs (Gordon, 2003), others have demonstrated that greenness could modify the air pollution and health relationship through different pollution mixtures, and increased overall health (e.g., physical activity, mental health and wellbeing) in ways that affect susceptibility (Son et al., 2021). Potential for non-linear or interactive effects on MetS due to multiple co-existing environmental stressors remains inconclusive. The joint analysis may contribute to identifying co-exposure factors with higher metabolic risk and further designing targeted and cost-effective interventions for them.

Therefore, this study aimed to examine the role of residential greenness and ambient temperature in modifying associations between long-term exposures to air pollutants and MetS in Chinese adults. We featured participants from a multi-ethnic cohort in Southwest China, where air pollution is severe and persistent during the unprecedented rapid urbanization and climate change (Kan et al., 2012; Song et al., 2017).

2. Methods

2.1. Study population

Our study population was drawn from the baseline survey of the China Multi-Ethnic Cohort (CMEC). A multi-stage stratified whole-group sampling method was used to obtain samples from community-based populations in five districts of southwest China. In the first stage, one or two minority settlements were selected as our study sites of each ethnic group. Special consideration was given to settlements in highlands, basins, rural areas, and areas with high air pollution to better reflect geography and development status. In the second phase, the local Centers for Disease Control and Prevention (CDC) selected 1–8 communities in each settlement (depending on community size), taking into account migration status, local health status, and, most importantly, ethnic structural bodies. In the final stage, participants who met our inclusion criteria were invited to participate in our study, taking sex ratios and age ratios into account. The inclusion criteria of the CMEC included (i) age 30–79 years on the day of the survey (except for the Tibetan population, whose age inclusion criterion was 18–79 years given the shorter life expectancy); (ii) permanent residents, with capacity to complete the baseline survey and the follow-up study; and (iii) completion of questionnaires, medical examinations, and blood tests. We invited participants in various ways, such as phone calls, social networking, and publicizing by local health authorities. From May 2018 through September 2019, a total of 99,556 adult participants aged 30–79 years were enrolled in the cohort study. The baseline survey included electronic questionnaires with face-to-face interviews, physical examinations and clinical laboratory tests. Ethical approval was granted by the Sichuan University Medical Ethical Review Board (K2016038). All individuals volunteered to participate in the study and signed a written informed consent prior to the start of the study. A more detailed description of this community-based cohort study is provided in a previously published study (Zhao et al., 2021).

We excluded residents in Tibet. The Tibetan population lives on a plateau above 3500 m above sea level, where the environment is extremely cold, with low atmospheric pressure and hypoxia. People living at high altitudes for long periods may display unique circulatory, metabolic, and hematological adaptations which may affect the comparability with populations in other regions (Beall, 2007; Bigham and Lee, 2014; Narvaez-Guerra et al., 2018). Moreover, the lower number of monitoring sites in Tibet (less than 20) affects the accuracy of exposure data measurements. In addition, participants were excluded if any of the criteria were present: (1) absence of available residential address information, and (2) resided at the current address for less than 3 years at the time of cohort entry, and (3) Tibetans in Aba because they were nomads without a fixed residence, and (4) diagnosed with malignancy or pregnancy, and (5) absence of any available information on outcome, exposure or adjusted covariates. The study population consisted of 72,278 participants after the exclusions (Fig. 1).

2.2. Measurement of MetS

We classified MetS based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Alberti et al., 2009). More precisely, MetS was defined as the presence of three or above of the following five risk factors: (1) elevated waist circumference (≥102 cm in males; ≥88 cm in females); (2) elevated triglycerides (TG) (≥1.7 mmol/L) or medication for elevated triglycerides; (3) reduced high density lipoprotein cholesterol (HDL-C) (<1.0 mmol/L in males; <1.3 mmol/L) in females) or medication for reduced HDL-C; (4) elevated blood pressure (systolic ≥130 or diastolic ≥85 mm Hg) or antihypertensive medication; (5) elevated fasting glucose (GLU) (≥5.6 mmol/L) or medication for elevated glucose. In the sensitivity analysis, we also classified MetS-China according to diagnostic criteria applicable to the Chinese population, which defines abdominal obesity as a lower waist circumference (≥85 cm in males; ≥80 cm in females).

The clinical and laboratory characteristics of participants were collected at the baseline survey. Blood pressures were measured by trained medical personnel using electronic sphygmomanometers. Systolic and diastolic blood pressures were taken as the average of three repeated measurements. Blood samples were taken from the antecubital vein after fasting for at least 8 h and tested for TG, HDL-C, and GLU by an AU5800 Automated Chemistry Analyzer (Beckman Coulter Commercial Enterprise, Shanghai, China).

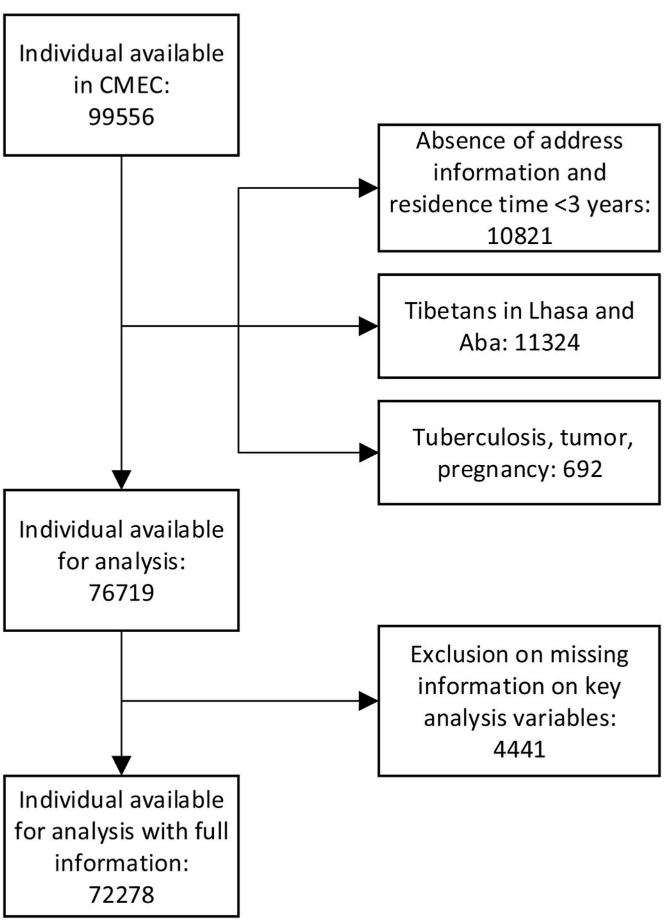

Fig. 1. Flow diagram for inclusion of exclusion criteria.

2.3. Environmental data

2.3.1. Air pollution

The study included two indicators of exposure to air pollution: $PM_{2.5}$ and O_3, which were obtained from the ChinaHighAirPollutants (CHAP) datasets (https://weijing-rs.github.io/product.html). Combined with satellite-derived aerosol optical depth (AOD) and ground-based monitoring data, the daily concentrations of $PM_{2.5}$ at a 1 km × 1 km resolution and O_3 at a 25 km × 25 km were estimated using Space-Time Extra-Trees (STET) model. Previous research shows that the data sets have good predictability for $PM_{2.5}$ and O_3 with 10-fold cross-validation R^2s of 0.90 and 0.84 respectively (Wei et al., 2019, 2020, 2021a, 2021b, 2021b). Based on geocoding matched by the residential address, the average concentrations of two air pollutants in the three years before participating in the baseline survey were calculated as a substitute for long-term exposure to air pollutants for each individual. The selection of a three-year exposure window was consistent with most cross-sectional studies (Cai et al., 2016).

2.3.2. Residential greenness

The green metric was used to assess exposure to residential greenness: the Normalized Difference Vegetation Index (NDVI), which was derived from Moderate-resolution Imaging Spectroradiometer (MODIS) images collected by the National Aeronautics and Space Administration's Terra satellite. MODIS offers gridded NDVI values at a 250 × 250 m spatial resolution every 16 days since 2000. NDVI was evaluated based on the land surface reflectance of near-infrared and visible red lights and is sensitive to seasonal changes in vegetation, land cover, and biophysical parameters (Meroni et al., 2019). Values of NDVI range from −1 to 1, with higher positive values corresponding to higher greenness. Negative values were recoded to zero before further analyses are conducted. We calculated the average NDVIs in the three years before the baseline survey within buffers with radii of 250 m for each participant's residential address.

2.3.3. Ambient temperature

Temperature data were obtained from the Integrated Forecast System (IFS) of the European Center for Medium-Range Weather Forecasts (ECMWF) (https://www.ecmwf.int/). Atmospheric model data sources include direct or ground-based observations such as ground-based weather stations, and indirect or satellite-based observations. The spatial scale of the temperature data is 0.1° × 0.1°. This study used 2 m air temperature (T2m) to assess ambient temperature exposure. Values of T2m were computed via interpolation between surface temperature and the level of the lowest atmospheric model level. We also obtained the average temperatures in the three years before the baseline survey for all addresses in the study.

2.4. Covariates

Covariates were chosen as potential confounders between exposures and outcomes or predictors of outcomes derived from the baseline survey. Demographic data included sex, age, rural/urban (rural, urban), district (Guizhou, Sichuan, Yunnan, Chongqing), ethnicity (Han, minority), marital status (married/cohabiting, others), and socioeconomic factors including education (elementary school or below, middle or high school, college school or above), annual family income ([¥], <20,000, 20,000–100,000, ≥100,000). Behavioral covariates included smoking status (non-smoker, current-smoker, previous-smoker), alcohol consumption (never, low/moderate, high), Mediterranean diet (MED) score, physical activity (low, moderate, high), secondary smoke (yes, no). MED diet pattern is the most studied a priori dietary pattern associated with cardiometabolic diseases (Trichopoulou et al., 2003).

2.5. Statistical methods

The Spearman correlations were calculated to evaluate the relations between the exposure variables. The study performed single-exposure models using logistic regression to investigate associations of each air pollutant ($PM_{2.5}$, O_3) and MetS, adjusted for covariates. The models included thirteen covariates (age, sex, rural/urban, district, ethnicity, income, education, marital status, smoking status, alcohol consumption, Mediterranean diet score, physical activity, secondary smoke). Two-exposure models were used to evaluate potential mutual confounding of residential greenness and temperature. We assessed whether the estimated association of the target variable (i.e., $PM_{2.5}$) is sensitive to extra-adjustment of another exposure variable (i.e., NDVI 250 m) using two-exposure models. In addition, we characterized the dose-response relationship by using spline models with 3 knots to determine the linearity of the exposure-response relationship by replacing the linear terms of the exposure variables with the thin-splines terms.

To evaluate whether temperature and green space alter the potential impacts of air pollutants, we examined the interaction effects of air pollutants ($PM_{2.5}$, O_3) with temperature and NDVI 250 m, respectively, both on multiplicative and additive scales. Interaction on a multiplicative scale or an additive scale suggests that the combined effect of the two variables is greater/less than the product or sum of their individual effects (Knol et al., 2011; Knol and VanderWeele, 2012). Interaction on the multiplicative scale was assessed by consisting of a product term for two exposure variables in the two-exposure model. We further assessed the interaction effect on the additive scale. Two categorical variables were generated using continuous variables of NDVI 250 m and temperature, with cut-off values in tertile. Participants with high NDVI 250 m level or low-temperature level were selected as the reference subgroups. We calculated the relative excess risk due to interaction (RERI) to estimate the additive interaction using a multiple logistic regression model (Hosmer and Lemeshow, 1992; Knol et al., 2011). It was calculated as

$$\ln\left(\frac{p}{1-p}\right) = ln(odds) = \widehat{\beta_0} + \widehat{\beta_1}A + \widehat{\beta_2}B + \widehat{\beta_3}AB$$

$$RERI = exp(\widehat{\beta_1} + \widehat{\beta_2} + \widehat{\beta_3}) - exp(\widehat{\beta_1}) - exp(\widehat{\beta_2}) + 1$$

Here, $\widehat{\beta_1}$ is the coefficient of air pollutants ($PM_{2.5}$ or O_3), β2 is the coefficient of categorical NDVI 250 m or temperature, and β3 is the coefficient of their cross-product. 95% CI of the RERI were computed through bootstrapping 1000 times. A RERI of less than, equal to, or more than 0 suggests negative additive interaction (joint excess risk < sum of individual excess risks), no additive interaction (joint excess risk = sum of individual excess risks), or positive additive interaction (joint excess risk > sum of individual excess risks), respectively.

To examine the stability of the results, we conducted sensitivity analyses by (1) not adjusting for district; (2) redefining MetS-China according to guidelines for the Chinese population; (3) excluding participants with self-reported hypertension and diabetes. We also performed subgroup analyses to evaluate associations of air pollutants with MetS by different districts and the stratification of air pollutants with temperature and greenness to MetS varied by sex.

The complete statistical analyses were done with R version 4.0.5 and significance was set at $P < 0.05$.

3. Results

3.1. Demographic characteristics

In total, our study population consisted of 72,278 individuals from

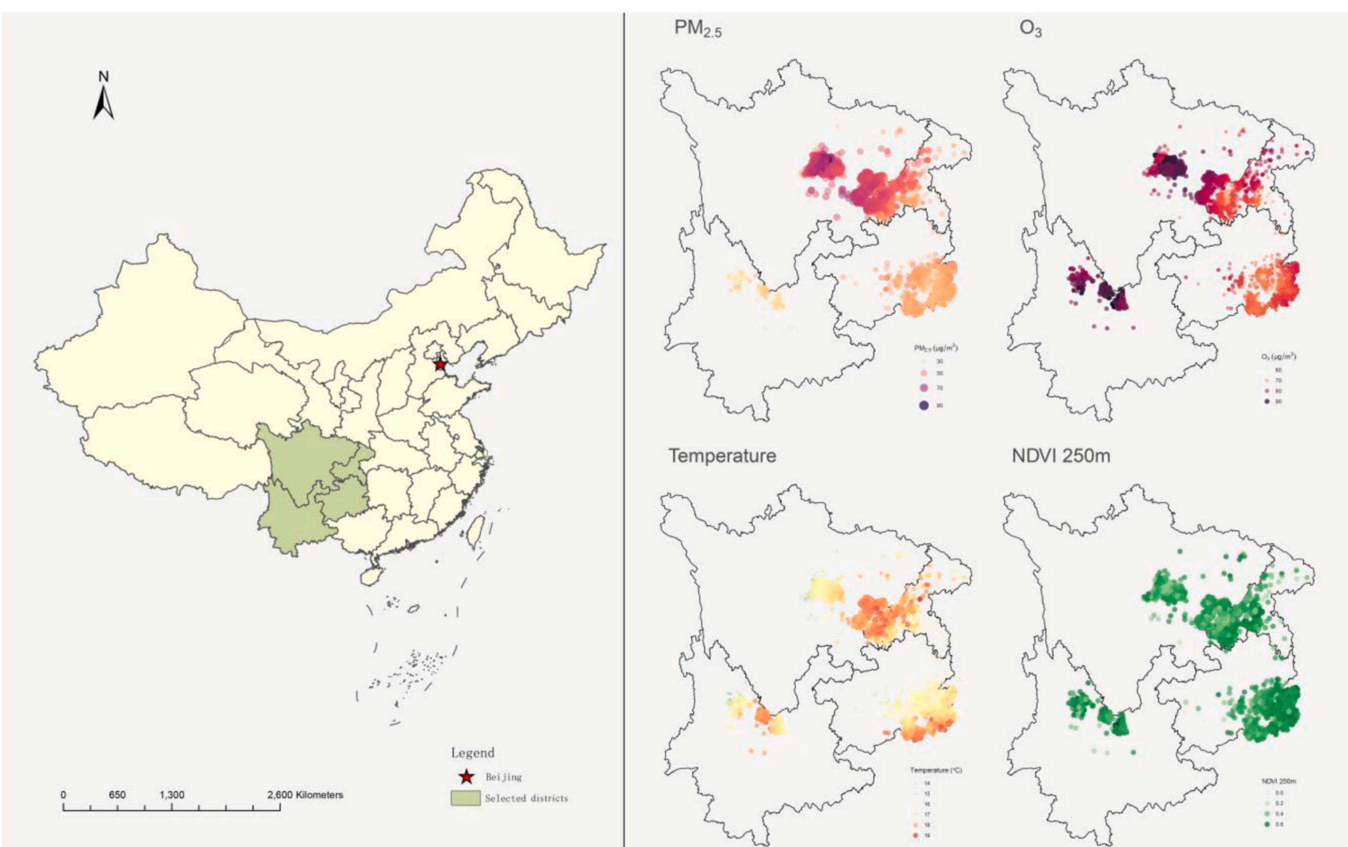

Fig. 2. Spatial distribution of participants with different environmental exposures in 4 districts. Darker spots indicate higher exposure doses. Abbreviations: $PM_{2.5}$, particular matter with aerodynamic diameter≤2.5 μm; NDVI 250 m, normalized difference vegetation index with a buffer of 250 m.

four districts in southwest China (Fig. 2). Table 1 shows the baseline characteristics of the study participants stratified by MetS. The population with a mean age of 52.22 (11.40) years was 60.2% female, and the overall MetS prevalence was 19.64% (14,194/72,278). Participants with MetS were, on average, older than those without MetS (55.98 versus 51.30 years), more likely to be female (62.8% versus 59.5%), had lower education and income level, and were more likely to consume alcohol.

Fig. 1 presented the spatial distribution of participants with different environmental exposures in 4 districts. Detailed exposure values for each district and the spearman correlations between the exposure variables were shown in supplementary materials (Table S1-S2). The environmental variables were set to the mean exposure values for three years before the baseline survey. The median (IQR) estimates of $PM_{2.5}$, O_3, NDVI 250 m, and temperature were 38.55 (29.55) μm/m^3, 79.92 (14.23) μm/m^3, 0.42 (0.22), and 17.08 (1.94) °C, respectively, among participants without MetS; and the corresponding estimates were 38.73 (29.04) μm/m^3, 78.50 (14.23) μm/m^3, 0.41 (0.22), and 17.17 (1.8) °C for those with MetS (Table 1). Descriptive characteristics of the five components of metabolic syndrome were shown in Table S3.

Table 1
Descriptive characteristics for the 72,278 participants by metabolic syndrome (MetS).

	Overall (N = 72,278)	Not MetS (N = 58,084)	MetS (N = 14,194)
Demographics			
Age (mean (SD))	52.22 (11.40)	51.30 (11.39)	55.98 (10.66)
Sex, n (%)			
Female	43,481 (60.2)	34,571 (59.5)	8910 (62.8)
Male	28,797 (39.8)	23,513 (40.5)	5284 (37.2)
Rural/urban, n (%)			
Rural	45,775 (63.3)	36,823 (63.4)	8952 (63.1)
Urban	26,503 (36.7)	21,261 (36.6)	5242 (36.9)
District, n (%)			
Guizhou	15,367 (21.3)	12,153 (20.9)	3214 (22.6)
Sichuan	17,559 (24.3)	14,176 (24.4)	3383 (23.8)
Yunnan	20,418 (28.2)	16,606 (28.6)	3812 (26.9)
Chongqing	18,934 (26.2)	15,149 (26.1)	3785 (26.7)
Ethnicity, n (%)			
Han	46,012 (63.7)	37,207 (64.1)	8805 (62.0)
Minority	26,266 (36.3)	20,877 (35.9)	5389 (38.0)
Marital status, n (%)			
Married/cohabiting	64,454 (89.2)	52,144 (89.8)	12,310 (86.7)
Single/divorced/ widowed/separated	7824 (10.8)	5940 (10.2)	1884 (13.3)
Education, n (%)			
Elementary school or below	35,209 (48.7)	27,461 (47.3)	7748 (54.6)
Middle or high school	28,654 (39.6)	23,421 (40.3)	5233 (36.9)
College school or above	8415 (11.6)	7202 (12.4)	1213 (8.5)
Annual family income, ¥ [a], n (%)			
<20,000	25,163 (34.8)	20,023 (34.5)	5140 (36.2)
20,000-100 k	37,099 (51.3)	29,868 (51.4)	7231 (50.9)
≥100 k	10,016 (13.9)	8193 (14.1)	1823 (12.8)
Behavioral factors			
Smoking status, n (%)			
Non-smoker	53,478 (74.0)	42,818 (73.7)	10,660 (75.1)
Current-smoker	15,126 (20.9)	12,337 (21.2)	2789 (19.6)
Previous-smoker	3674 (5.1)	2929 (5.0)	745 (5.2)
Alcohol consumption, n (%)			
Never	40,145 (55.5)	31,720 (54.6)	8425 (59.4)
Low/moderate	24,512 (33.9)	20,151 (34.7)	4361 (30.7)
High	7621 (10.5)	6213 (10.7)	1408 (9.9)
Physical activity, n (%)			
Low	42,093 (58.2)	34,476 (59.4)	7617 (53.7)
Moderate	9826 (13.6)	8089 (13.9)	1737 (12.2)
High	20,359 (28.2)	15,519 (26.7)	4840 (34.1)
Mediterranean diet score (mean (SD))	24.85 (4.43)	24.85 (4.43)	24.85 (4.43)
Secondary smoke, n (%)			
Yes	37,315 (51.6)	30,097 (51.8)	7218 (50.9)
No	34,963 (48.4)	27,987 (48.2)	6976 (49.1)
Environmental exposures			
$PM_{2.5}$, (μm/m3), (median [IQR])	38.55 (29.48)	38.55 (29.55)	38.73 (29.04)
O_3, (μm/m3), (median [IQR])	79.03 (14.23)	79.92 (14.23)	78.50 (14.23)
NDVI 250 m (median [IQR])	0.42 (0.22)	0.42 (0.22)	0.41 (0.22)
Temperature, (°C), (median [IQR])	17.09 (1.94)	17.08 (1.94)	17.17 (1.8)

Abbreviations: MetS, metabolic syndrome; SD, standard deviation; IQR, inter-quartile range; $PM_{2.5}$, particular matter with aerodynamic diameter≤2.5 μm; NDVI 250 m, normalized difference vegetation index with a buffer of 250 m.
[a] $1.00 was equivalent to ¥6.62 in 2018 and ¥6.90 in 2019.

3.2. Association between each air pollutant exposure and MetS

The associations between each air pollutant exposure and MetS are presented in Table 2. We observed that $PM_{2.5}$ and O_3 were each associated with an increased OR of MetS in the models after adjusting for covariates. The ORs (95% CI) of MetS for an IQR increase in $PM_{2.5}$, O_3 were 1.38 (1.23, 1.55) and 1.15 (1.09, 1.22). Table 2 also presents similar results of adjusting NDVI or temperature as a confounder, showing that robustness. The association of $PM_{2.5}$ with MetS attenuated moderately when adjusted for NDVI, and temperature with ORs (95% CI) decreased from 1.38 (1.23, 1.55) per IQR increment to 1.32 (1.18, 1.49), and 1.34 (1.2, 1.5) separately. Estimated exposure-response curves for MetS are shown in Fig. S1.

3.3. Joint associations of environmental exposures with MetS

Table 3 shows odds ratios for air pollutants with the prevalence of MetS for each stratum of temperature and the interaction effects of air pollutants with temperature respectively on MetS. Specifically, the OR of MetS for each IQR increase in $PM_{2.5}$ was 1.36 (95% CI 1.05, 1.76) for people who were exposed to the low temperature level, 1.34 (1.13, 1.6) for the medium temperature level, and 1.23 (1.02, 1.48) for the high temperature level. The OR of MetS for each increase in IQR of O_3 for people exposed to different temperature levels was 1.05 (95% CI 0.99, 1.11), 0.95 (0.79, 1.14) and 1.13 (1.06, 1.21), respectively. The multiplicative interactions, by temperature, for the associations of $PM_{2.5}$ ($P_{interaction} < 0.001$) and O_3 ($P_{interaction} < 0.001$) with MetS were significant (Table S4). On the additive scale, the interaction was statistically significant between $PM_{2.5}$ and temperature on MetS (RERI: 0.40, 95% CI: 0.01, 11.88). The interactions of $PM_{2.5}$ and O_3 with high temperature level respectively on MetS were statistically significant (RERI = −0.22 [95% CI: 0.44, −0.04]; 0.05 [0.02, 0.11]) with participants in low temperature level as the reference group. A RERI of −0.22 means that the relative risk of having MetS with high temperature is 0.22 less with each IQR increase in $PM_{2.5}$ than if there were no interaction between

Table 2
Odds ratios of metabolic syndrome associated with each IQR increase of air pollutants ($PM_{2.5}$, O_3) from single- and two-exposure models.

Exposure variable	OR (95% CI)[a] for an IQR increase		
	Single exposure	Two exposures (adj. for)	
		NDVI 250 m	Temperature
$PM_{2.5}$	1.38 (1.23, 1.55)	1.32 (1.18, 1.49)	1.34 (1.20, 1.50)
O_3	1.15 (1.09, 1.22)	1.17 (1.10, 1.24)	1.12 (1.05, 1.19)

N = 72,278.
Abbreviations: OR, odds ratio; CI, confidence interval; IQR, inter-quartile range; NDVI 250 m, normalized difference vegetation index with a buffer of 250 m; $PM_{2.5}$, particular matter with aerodynamic diameter ≤ 2.5 μm.
Bold indicates statistically significant results $P < 0.05$.
IQR for $PM_{2.5}$: 29.48 μg/m^3, O_3: 14.23 μg/m.^{3}.
[a] Adjusted for confounders (age, sex, rural/urban, district, ethnicity, income, education, marital status, smoking status, alcohol consumption, Mediterranean diet score, physical activity, secondary smoke).

Table 3
Odds ratios for metabolic syndrome according to $PM_{2.5}$ or O_3 by temperature.

Air pollutants	Low temperature (13.5, 16.6]	Medium temperature (16.6, 18]	High temperature (18, 19.3]
	OR (95% CI)[a]	OR (95% CI)	OR (95% CI)
$PM_{2.5}$ (Per IQR)	**1.36 (1.05, 1.76)**	**1.34 (1.13, 1.6)**	**1.23 (1.02, 1.48)**
RERI (95% CI)[b]	-	−0.07 (−0.21, 0.05)	**−0.22 (-0.44, -0.04)**
O_3 (Per IQR)	1.05 (0.99, 1.11)	0.95 (0.79, 1.14)	**1.13 (1.06, 1.21)**
RERI (95% CI)		−0.08 (−0.36, 0.03)	**0.05 (0.02, 0.11)**

Abbreviations: OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction; NDVI 250 m, normalized difference vegetation index with a buffer of 250 m; $PM_{2.5}$, particular matter with aerodynamic diameter≤2.5 μm. Bold indicates statistically significant results $P < 0.05$.
IQR for $PM_{2.5}$: 29.48 μg/m^3, O_3: 14.23 μg/m.^{3}.
[a] The models were fully adjusted for age, sex, rural/urban, district, ethnicity, income, education, marital status, smoking status, alcohol consumption, Mediterranean diet score, physical activity, secondary smoke.
[b] The RERIs and their 95% CIs were calculated using each IQR increase in air pollutants ($PM_{2.5}$ or O_3) and levels of temperature.

$PM_{2.5}$ and high temperature. The RERI of 0.05 means that the relative risk of having MetS with high temperature is 0.05 more with each IQR increase in O_3 than if there were no interaction between O_3 and high temperature.

Table 4 represents the associations between air pollutants and MetS stratified by NDVI 250 m and the interaction effects of air pollutants with NDVI 250 m respectively on MetS. The OR of MetS for each IQR increase in $PM_{2.5}$ was 1.08 (95% CI 0.99, 1.17) for people who were exposed to the high NDVI 250 m level, 1.43 (1.12, 1.81) for the NDVI 250 m level, and 1.47 (1.18, 1.82) for the low NDVI 250 m level. The OR of MetS for each increase in IQR of O_3 for people exposed to different NDVI 250 m levels was 1.15 (95% CI 1.03, 1.27), 1.16 (1.04, 1.29) and 1.23 (1.10, 1.38), respectively. The multiplicative interactions, by NDVI 250 m, for the associations of $PM_{2.5}$ ($P_{interaction}$ <0.001) with MetS were significant (Table S4). Significant interaction on the additive scale was observed between $PM_{2.5}$ and NDVI 250 m on MetS (RERI = 0.13 [95% CI: 0.05, 0.19]) with participants in high NDVI 250 m level as the reference group, which means that the relative risk of having MetS among low NDVI 250 m level is 0.13 more with each IQR increase in $PM_{2.5}$ than if there were no interaction. However, no significant interaction was observed on both multiplicative and additive scale between O_3 and NDVI 250 m on MetS.

Sensitivity analyses showed that the estimated ORs of MetS for air pollutant exposures became lower without adjusting for district and the results for O_3 lost statistical significance (Table S5). Sensitivity analyses for interaction analyses did not materially change our findings (Table S6-S11). In the district-specific subgroup analyses (Table S12), the ORs (95% CIs) of MetS for $PM_{2.5}$ were 1.11 (1.07, 1.14) and 1.19 (1.14, 1.25) in Sichuan and Yunnan province. The ORs (95% CIs) of MetS for O_3 were 1.15 (1.12, 1.18) and 1.10 (1.02, 1.19) in Yunnan and Chongqing province. In the gender-specific subgroup analyses (Table S13-S15), we observed significant interactions between $PM_{2.5}$ and NDVI 250 m on additive and multiplicative scales only in females. The results for males showed interactions between air pollutants and temperature in the consistent direction of the pool analysis, but lost statistical significance.

Table 4
Odds ratios for metabolic syndrome according to $PM_{2.5}$ or O_3 by NDVI 250m.

Air pollutants	High NDVI 250 m (0.47, 0.74]	Medium NDVI 250 m (0.33, 0.47]	Low NDVI 250 m (0, 0.33]
	OR (95% CI)[a]	OR (95% CI)	OR (95% CI)
$PM_{2.5}$ (Per IQR)	1.08 (0.99, 1.17)	**1.43 (1.12, 1.81)**	**1.47 (1.18, 1.82)**
RERI (95% CI)[b]	–	**0.1 (0.03, 0.16)**	**0.13 (0.05, 0.19)**
O_3 (Per IQR)	**1.15 (1.03, 1.27)**	**1.16 (1.04, 1.29)**	**1.23 (1.10, 1.38)**
RERI (95% CI)	–	0.01 (−0.02, 0.05)	0.03 (−0.01, 0.09)

Abbreviations: OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction; NDVI 250 m, normalized difference vegetation index with a buffer of 250 m; $PM_{2.5}$, particular matter with aerodynamic diameter≤2.5 μm. Bold indicates statistically significant results $P < 0.05$.
IQR for $PM_{2.5}$: 29.48 μg/m^3, O_3: 14.23 μg/m.^{3}.
[a] The models were fully adjusted for age, sex, rural/urban, district, ethnicity, income, education, marital status, smoking status, alcohol consumption, Mediterranean diet score, physical activity, secondary smoke.
[b] The RERIs and their 95% CIs were calculated using each IQR increase in air pollutants ($PM_{2.5}$ or O_3) and levels of NDVI 250 m.

4. Discussion

This work is the first epidemiological research to evaluate the associations between joint exposure to various environmental factors and MetS in developing countries to the best of our knowledge. The constellation of findings suggested that exposure to higher air pollutants levels was associated with MetS. We also observed significant interactions between air pollutants ($PM_{2.5}$, O_3) and temperature exposure on MetS at both multiplicative and additive scales. More specifically, interactions showed that $PM_{2.5}$ is more strongly associated with MetS at a lower temperature, while O_3 is more strongly linked with MetS at a higher temperature. We also observed interaction between $PM_{2.5}$ and greenness at both multiplicative and additive scales but no interaction between O_3 and residential greenness.

In this work, we found that air pollutants ($PM_{2.5}$, O_3) were associated significantly with MetS, which was in accordance with previous findings (Wallwork et al., 2017; Yang et al., 2018). A number of epidemiological studies have observed the long–term associations between air pollutants and metabolic diseases (Yang et al., 2018; Yu et al., 2020). Several hypotheses have been proposed to explain the effects of air pollution, especially $PM_{2.5}$, on metabolic health. First, air pollutants could increase oxidative stress and inflammation in the lungs. Some pollutants can also migrate through the lung epithelium into the bloodstream. These pathways may lead to systemic and vascular inflammation, increasing the risk of dyslipidemia, hypertension and thrombosis (Wei et al., 2016; Xu et al., 2011). Other evidence also found that environmental PM induces DNA hypomethylation, associated with increased blood pressure (Bellavia et al. n.d.).

Research from developing countries reported a higher prevalence of metabolic syndrome and more severe air pollution concentrations than studies from developed regions. However, previous studies frequently investigated the effects of air pollutants on MetS with little consideration of its joint association with ambient temperature and greenness. The only one evaluated the associations between MetS and multiple air pollutants while including greenness as a confounder (Voss et al., 2021). Evidence of potential interaction between air pollutants with environmental factors has emerged in studies on other health outcomes (Garcia-Menendez et al., 2015; Ji et al., 2020; Orru et al., 2013).

The main contribution of this work to the published literatures is the statistically significant interaction between air pollution and ambient temperature on MetS. Our study found that individuals living in areas with lower temperatures appear to be affected more by $PM_{2.5}$. This work suggests that reducing the concentration of particulate matter in a cold climate may have a synergistic effect on metabolic health, with greater health benefits than controlling particulate matter separately. Although the exact mechanisms remain to be elucidated, a possible explanation is that ambient temperature could be a primary driver of fine particle composition and the different particulate compositions may lead to different toxicity. Lower temperatures are linked to higher nitrate concentrations, while sulfate levels increased for higher temperatures (Kavouras and Chalbot, 2017). In addition, an extensive systematic review in humans has assembled physiological evidence that cold temperatures induce supersaturated conditions in airways, consequently enhancing pulmonary particulate deposition (Ishmatov, 2020). Similar evidence was found in short-term studies on metabolic-related diseases and respiratory diseases, such as respiratory inflammation and chronic obstructive pulmonary disease (COPD) (Li et al., 2017; Qiu et al., 2018; Wu et al., 2015; Zhang et al., 2015).

Our findings of interaction between ozone and temperature on MetS were in line with most current studies that ozone effects were worse at the higher temperature (Lim et al., 2019; Orru et al., 2019; Ren et al., 2008). One study assessed the acute impact of ozone, heat, and their interaction, on mortality in 15 British conurbations though the interaction was significant in London only (Pattenden et al., 2010). Significant environmental temperature changes may lead to physiological and psychological stress, which can alter an individual's physiological response to toxic agents (Jörres et al., 2000). Also, recent literature explained the acute effects of temperature and ozone on heart rate variability, of which imbalance has been linked to adverse cardiovascular outcomes (Tang et al., 2021; Thayer et al., 2010; Wang et al., 2022). Ambient temperature and ozone might interact to affect cardiovascular function via the autonomic nervous system (Ren et al., 2011). This study provides new evidence that long-term co-exposure to high levels of temperature and ozone may lead to synergistic effects, especially on metabolic diseases.

The negative modification of greenness on the association between $PM_{2.5}$ and MetS was observed in this study, similar to the findings of some previous studies exploring how green space affects the health effects of PM. However, the results of previous studies are mixed with no consensus on the role of green as a buffer against air pollution-related exposure pathways (Ji et al., 2020; Kim et al., 2019; Sun et al., 2020). After adjusting for various personal and contextual characteristics in analyses, it remains possible that there were differences in mental health or stress levels and susceptibilities to the effects of exposure among people living in different green spaces (Dadvand et al., 2016). There may also be important differences in particulate matter components and pollutant sources between more and less green areas. Studies have previously suggested that $PM_{2.5}$ composition varies with local traffic, human activities, and industrial land-use, which are also associated with green vegetation fraction (Bell et al., 2007; Hu et al., 2009). Based on the complexity of the mechanism and the structural diversity of green space, further research on metabolic diseases with more precise data is needed to comprehensively understand the interaction between air pollution and green space.

Sensitivity and stratification analyses suggested the importance of the district in the relationship between air pollution and MetS. The district variable could partially reflect area-level socioeconomic status (SES), which is a key confounder in epidemiological studies of air pollution and health (Hajat et al. n.d.). The associations between air pollutants and MetS differ across districts. This variability may be attributed to socioeconomic status varying across the province or differences in particulate matter composition (Bell and Ebisu, 2012). An increasing number of studies have included gender in their analyses to explore its effect modifications. In this study, we found that the interaction of air pollutants and ambient temperature or greenness on MetS differed by gender. Such difference could be explained by exposure patterns (e.g. activity patterns, co-exposures, or exposure measurement accuracy) and sex-linked biological responses (e.g. lung volume, deposition, and hormonal influences on chemical transport and systemic regulation) proposed in previous evidence (Clougherty, 2010). Disentangling these effects is challenging yet necessary for fully understanding the relevant pathways for differential environmental effects on health.

The interaction results for the multiplicative and additive scales in this work were consistent in direction but differ in statistical significance, which reflects the fact that interaction is scale-dependent (Knol and VanderWeele, 2012). It is always best for both to be reported generally because both can be informative. For public health interventions, interactions on additive scale quantitatively show which subpopulation is more vulnerable to the environmental risk factor, which is important in resource allocation and in targeting specific populations for public health policy, and thus relevant also for cost-effectiveness (Greenland, 2009; Knol and VanderWeele, 2012).

This study also has several limitations. First, this cross-sectional study could not make inferences of causal associations. Second, our exposure datasets did not include information on time spent in traffic or outdoors, nor did they contain information on potential contact with indoor exposures, which might introduce misclassification bias. Third, we obtained an overall green cover area from NDVI without information of specific vegetation type, which may ignore the differences in effects due to different vegetation. Fourth, the exclusion of residents who had lived in their current residence for less than three years may reduce the generalizability of this work, but it also reduces the misclassification bias. In addition, the composition of $PM_{2.5}$ was not available, which might vary by region and over time and the spatial resolution of air pollution measures is not fine enough. Finally, although this study examined and compared the association of four widely studied environmental factors with metabolic syndrome, we may still have overlooked associations between other environmental exposures and metabolic health.

In addition to the limitations mentioned above, this study also has several strengths. Our large population size, high quality of the data, and well-examined participants ensured the validity of the results. Specifically, The baseline survey of CMEC was based on the standardized survey approach and multiple stringent quality control (QC), such as the interviewer-administered electronic questionnaire with real-time audio recording, and the cohort-developed online system allowing for retrospective access (Sun et al., 2022). We had detailed demographic and behavioral information, allowing to control for confounding factors as comprehensively as possible.

5. Conclusion

Collectively, this study provides suggestive evidence for the joint associations of ambient air pollutants ($PM_{2.5}$, O_3), ambient temperature and residential greenness with MetS based on a large population sample from the CMEC cohort study. Our findings suggested that long-term exposure to higher temperature might attenuate the association between $PM_{2.5}$ and MetS, while enhancing the association between O_3 and MetS. Thus, ambient temperature should be considered in the assessment of air pollutants' effects. Increased greenness may also weaken the relationship between $PM_{2.5}$ and MetS. Our findings could help explain the complexities underlying the epidemiological linkage between metabolic syndrome and multiple environmental factors. These findings may also have public health implications for future policies to mitigate environmentally induced health risks that would benefit from broader coordination.

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.envres.2022.113699.

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