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Associations of long-term exposure to ambient ozone with hypertension, blood pressure, and the mediation effects of body mass index: A national cross-sectional study of middle-aged and older adults in China

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ABSTRACT

Background: The associations between long-term exposure to ozone (O_3) and respiratory diseases are well established. However, its association with cardiovascular disease (CVD) remains controversial. In this study, we examined the associations between O_3 and the prevalence of hypertension and blood pressure, and the mediation effects of body mass index (BMI) in Chinese middle-aged and older adults.

Methods: In this national cross-sectional study, we estimated the O_3 exposure of 12,028 middle-aged and older adults from 126 county-level cities in China, using satellite-based spatiotemporal models. Generalized linear mixed models were used to evaluate the associations of long-term exposure to O_3 with hypertension and blood pressure, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP). Mediation effect models were applied to examine the mediation effects of BMI among O_3-induced hypertension and elevated blood pressure.

Results: Each 10 $\mu g/m^3$ increase in O_3 concentration was significantly associated with an increase of 13.7% (95% confidence interval (CI): 4.8%, 23.3%) in the prevalence of hypertension, an increase of 1.128 mmHg (95% CI: 0.248, 2.005), 0.679 mmHg (95% CI: 0.059, 1.298), 0.820 mmHg (95%CI: 0.245, 1.358) in SBP, DBP, and MAP, respectively. Mediation effect models showed that BMI played 40.08%, 37.25%, 39.95%, and 33.51% mediation roles in the effects of long-term exposure to O_3 on hypertension, SBP, DBP, and MAP, respectively.

Conclusions: Long-term exposure to O_3 can increase the prevalence of hypertension and blood pressure levels of middle-aged and older adults, and an increase of BMI would be an important modification effect for O_3-induced hypertension and blood pressure increase.

1. Introduction

Hypertension, characterized by elevated blood pressure, is one of the most noticeable risks for cardiovascular disease (CVD), leading to functional or organic damage to the heart, brain, kidney, and other organs (Ettehad et al., 2016; Zhou et al., 2021a). High systolic blood pressure (SBP) has been identified as the leading risk factor for all-cause deaths in China, accounting for 2.6 million deaths and 54.4 million disability-adjusted life lost years (DALYs) in 2019 (GBD, 2019). Epidemiological studies have confirmed that the prevalence of hypertension and high blood pressure for middle-aged and older people is higher than that among young participants (Niu et al., 2020; WHO, 2019). China has become a fast aging society since the end of the 20th Century and the proportion of the middle-aged and older population will continue to rise in the next few decades (Fang et al., 2020; Zhang et al., 2020). The proportion of the population aged 65 years and above will reach 14% in 2025 and about 30% by 2050 (Zhang et al., 2020). Identification of the risk factors for hypertension is critical to promoting the health of the middle-aged and elder populations in China.

Despite great improvements in air pollution control since the Air

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Pollution Prevention and Control Action Plan (APPCAP, 2013), the annual concentration of ozone (O_3) has increased substantially (Huang et al., 2018a) and O_3 has been become a major problem that affects air quality for a long period (Wang et al., 2021). Compared with well-established relationship of O_3 with respiratory diseases (Paulin et al., 2020; Wang et al., 2019), the long-term effects of O_3 exposure on CVD are controversial (Day et al., 2017). As important predictors of CVD, whether blood pressure level and hypertension risk would increase when exposed to higher O_3 concentrations requires urgent exploration. Mechanistic evidence indicates that exposure to O_3 could trigger autonomic nervous system imbalance, systemic inflammation, and oxidative stress, eventually leading to evaluated blood pressure and hypertension (Bai et al., 2019; Huang et al., 2019; Song et al., 2020). Therefore, it has been hypothesized that exposure to O_3 might contribute to hypertension and elevated blood pressure levels. Many epidemiological studies have evaluated the long-term effects of O_3 on hypertension and blood pressure (Chuang et al., 2011; Dong et al., 2013; Weaver et al., 2021). However, consistent findings have not been obtained (Yang et al., 2018). For example, a meta-analysis found no significant association between long-term O_3 exposure and blood pressure (SBP, diastolic blood pressure (DBP)), and the effects of O_3 on hypertension were not pooled because of the limited number of studies (Yang et al., 2018). After Yang et al.'s study, the Jackson Heart Study reported significant associations of long-term exposure to O_3 with increased SBP, DBP, and mean arterial pressure (MAP), while no significant association was observed for hypertension (Weaver et al., 2021). In addition to the uncertainty in epidemiological findings, the majority of previous studies were conducted in developed countries and the general population, and little attention was paid to developing countries with worse air quality and middle-aged and older adults at high risk of hypertension (Li et al., 2019).

In addition, the number of overweight and obese middle-aged and elder adults has been increasing rapidly (Chooi et al., 2019), and the body mass index (BMI) has been implicated in numerous CVDs in recent research (Khan et al., 2018; Xing et al., 2020). Studies suggested that exposure to ambient O_3 was associated with overweight and obesity (Huang et al., 2020; Kim et al., 2019; Yang et al., 2019c), and a higher BMI was a crucial risk factor for hypertension and other cardiovascular diseases (Iida et al., 2019; Koman and Mancuso, 2017; Sagaro et al., 2021; Shore, 2019). For example, a Chinese national cross-sectional study of 13,414 respondents demonstrated that exposure to ambient O_3 was positively associated with BMI ($\beta = 0.021$; $p < 0.001$) (Yang et al., 2019c). Iida et al. suggested that each 1 kg increase in body weight was associated with a 0.52 mmHg increase in SBP (95% confidence interval (CI): 0.21, 0.84) and a 0.27 mmHg increase in DBP (95% CI: 0.06, 0.48) (Iida et al., 2019). Moreover, some studies found that BMI was an important modifier of the associations of air pollution with CVD, including blood pressure and hypertension (Dong et al., 2015; Yang et al., 2019b). For example, a cross-sectional study of 9354 Chinese children suggested that the estimated effects of air pollution (particles with an aerodynamic diameter ≤ 10 μm, PM_{10}; sulfur dioxide, SO_2, and O_3) on hypertension risk were consistently larger for overweight/obese children than for children with normal weight (Dong et al., 2015). However, those findings were all based on interaction analysis, and the proportion of the effect attributable to BMI was not evaluated. Mediation effect analysis decomposes the total exposure-outcome effect into a direct effect and an indirect effect through a mediator variable (Rijnhart et al., 2021; VanderWeele, 2014) and has already been used in studies of the short-term health effects of exposure to air pollution recently (Cong et al., 2022; Feng et al., 2021; Sun et al., 2020). However, the mediation effects have not been evaluated in the associations between long-term exposure to air pollution and health effects.

Therefore, to fill this gap, we conducted a national cross-sectional study of Chinese middle-aged and elder adults to explore the long-term effects of O_3 exposure on the prevalence of hypertension and blood pressure. Our study focused on the associations of O_3-hypertension, O_3-blood pressure, and the mediation effects of BMI in O_3-induced hypertension and blood pressure increase.

2. Methods

2.1. Study population

The study population was obtained from the China Health and Retirement Longitudinal Study (CHARLS), which was established to collect a high-quality nationally representative sample of Chinese residents aged 45 and older (Zhao et al., 2014). In brief, participants were recruited randomly using a multi-stage stratified probability proportionate to size sampling (PPS) method, and the sample range covered 450 communities in 150 county-level cities of 28 Chinese provinces. Four national surveys were completed in 2011, 2013, 2015, and 2018. Blood pressure and other physical examinations were only completed in 2011 (Wave 1) and 2015 (Wave 3). Ground-based measurements and other required information used in O_3 assessment were mainly conducted after 2013 in China (Huang et al., 2018b); therefore, we enrolled the 16,361 participants in CHARLS wave 3 who had completed blood pressure measurements into our study. Participants were excluded if they smoked, exercised, or consumed alcohol or food within the 30 min before the blood pressure test, with missing or abnormal height and weight, blood pressure data, and without O_3 exposure assessments. The flowchart for participant enrollment is shown in Fig. S1. Eventually, a total of 12,208 middle-aged and older adults were included in the study. The Institutional Review Board at Peking University approved the CHARLS study (Code: IRB00001052–11015) and informed consent was signed before the investigation by each participant.

2.2. Assessment of blood pressure and hypertension

Hypertension cases were defined as individuals having any of the following conditions: (1) Systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg; (2) having self-reported clinically diagnosed hypertension or anti-hypertension drug intake (Li et al., 2019). Blood pressure was evaluated using an electronic monitor (HEM-7200 Monitor, Omron, Kyoto, Japan) on the left arm, and participants were asked to keep seated and remain quiet during the three assessments times. Blood pressure levels were calculated by averaging the three measurements. Mean arterial pressure (MAP) was calculated as DBP + 1/3 (SBP - DBP), and pulse pressure (PP) was calculated as SBP – DBP (Darne et al., 1989).

2.3. Assessment of O_3 exposure

Full-coverage ground-level maximum 8-hour average (MDA8) O_3 concentrations in China (ChinaHighO_3),estimated using artificial intelligence at a 0.1 degree (≈ 10 km) gridded spatial resolution from 2013 to 2015, were collected from the CHAP dataset (available at https://weijing-rs.github.io/product.html). Details of the estimation method have been published in our previous study (Wei, 2022). In brief, a space-time extremely randomized trees (STET) model was employed to estimate ground-level O_3 concentrations using ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and emission inventory. Our estimates for the whole of China were highly consistent with surface measurements, with a coefficient of determination (R^2) of 0.87 and root-mean-square error (RMSE) of 17.10 μg/m^3. Each individual's O_3 exposure was assessed according to residential addresses at the county level. Three-year average O_3 exposure of each participant before CHARLS wave 3 were calculated as long-term O_3 exposure in our current study (Mao et al., 2020), while 2-year average and 1-year average O_3 exposure was employed in the sensitivity analyses.

2.4. Assessment of mediation variables

Height was examined using a stadiometer, and participants were asked to stand erect on the floorboard of the stadiometer with their back to the vertical backboard stadiometer and maintained their head in the Frankfort Horizontal Plane position. Individual weight was measured using scales, in a standing position with their shoes off. We then the BMI as a mediation variable for further statistical analysis (Peterson et al., 2016).

2.5. Statistical analysis

Generalized linear mixed models (GLMMs) were employed to investigate the associations of O_3 exposure with hypertension and blood pressure (Li et al., 2020). To account for repeated measurements from the potential regional discrepancy, community ID was included in models as a random effect term (Li et al., 2020; Lin et al., 2017; Yao et al., 2022). The effect estimates and 95% CIs were presented as percentage changes (%) for the prevalence of hypertension and changes in mmHg for blood pressure per 10 μg/m^3 in the O_3 concentration.

We identified potential confounders as common causes of hypertension and air pollution in the literature (Li et al., 2019, 2020; Liu et al., 2019a, 2021; Schisterman et al., 2009), including temperature, humidity, age, gender (“Male” or “Female”), BMI, residence (“Urban” or “Rural”), marital status (“Married and living with spouse” or “Married but living without spouse” or “Single, divorced, and widowed”), smoking status (“Non-smoker” or “Smoker”), and drinking status (“Non-drinker” or “Drink but less than once a month” or “Drink more than once a month”). Then we developed a directed acyclic graph (DAG, Fig. S2) to retain the minimally sufficient set of covariates to adjust for confounding factors (Greenland et al., 1999), including temperature, humidity, age, gender, residence, marital status, smoking status, and drinking status. For smoking status, smokers were defined as individuals who chewed tobacco, smoked a pipe, self-rolled cigarettes, cigarettes, or cigars. Drinking status was assessed by investigating the alcohol consumption of each participant in the past year and alcohol types included liquor, wine, or beer. Sociodemographic and socioeconomic variables (age, gender, residence, marital status) and health behavior variables (smoking status and drinking status) were collected through face-to-face interviews. BMI was measured by physical examination, and annual temperature and humidity from 2013 to 2015 were obtained from China Meteorological Administration (http://www.cma.gov.cn). Briefly, we firstly initiated the model development with a crude model (no adjustment). Then adjusted model 1 was employed to adjust for temperature, humidity, age, gender, and residence. Finally, adjusted model 2 additionally adjusted for marital status, smoking status, and drinking status. BMI was not adjusted in the model as a confounder because it might be the mediation factor in air pollution-induced blood pressure change and hypertension (Schisterman et al., 2009; Yang et al., 2019a).

The mediation effect model was employed to examine the mediation effects of BMI among O_3-induced hypertension and blood pressure. Briefly, we firstly performed GLMM models of O_3 exposure and BMI (Model a), and then examined the association of O_3 exposure and hypertension or blood pressure with BMI as a covariate variable (Model b). Finally, the mediation effect model was applied to examine the mediation effects of BMI (Tingley et al., 2013).

In addition, we also examined the associations of O_3-hypertension and O_3-blood pressure among participants of different ages, gender, residence, marital status, smoking, drinking status, and geographical area by introducing an interaction term (Liu et al., 2017). Participants were grouped into elderly and middle-age groups with a cut-off of 65 years old in the subgroup analysis (Liu et al., 2019b). The geographical area was divided into the north area and south area according to the Qinling Mountains–Huaihe River line (Zhou et al., 2021b).

A series of sensitivity analyses were also performed to test the robustness of the results. Firstly, we re-performed the GLMM models and mediation analysis by using the 2-year and 1-year average concentrations of O_3 exposure before investigation. Secondly, we excluded individuals taking anti-hypertensive drugs to examine whether the associations between O_3 and blood pressure were altered by drug intake (Li et al., 2020). Thirdly, we conducted sensitivity analyses by excluding participants who had ever changed their residence from their last investigation in 2013. Finally, a 4-way decomposition median analysis was used to examine the robustness of the mediation analysis and identify whether interaction effects existed (Discacciati et al., 2018).

Apart from the 4-way decomposition median analysis, the statistical analyses were completed using R software version 4.1.2. The four-way decomposition median analysis was performed by “med4way” command in Stata 16.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Descriptive statistics

A total of 12,028 middle-aged and older adults were included in our study. Participants were obtained from 436 communities in 126 county-level cities of 27 Chinese provinces, and the distribution of the participants is shown in Fig. 1. The mean age of participants was 60.66 ± 9.68 years and their mean BMI was 23.87 ± 3.65 kg/m^2. Most participants were male (61.87%), lived in rural areas (62.31%), and were married and living with a spouse (82.51%). We identified 4586 (38.13%) hypertension cases, with 3456 participants diagnosed with hypertension and 2397 self-reported cases. Moreover, 2937 (64.04%) participants with hypertension were taking anti-hypertensive medication. Participants with hypertension tended to be older (63.23 years versus 59.09 years, $P < 0.001$) and have a higher BMI (24.75 kg/m^2 versus 23.34 kg/m^2, $P < 0.001$) (Table 1).

Table 2 presents the average levels of O_3, temperature, humidity, and blood pressure. The 3-year average O_3 exposure was 84.22 ± 7.19 μg/m^3. Temperature and humidity were 24.00 ± 15.57 ℃ and 69.43 ± 9.62%. The mean levels of SBP, DBP, MAP, and PP were 128.50 ± 19.90 mmHg, 75.71 ± 11.68 mmHg, 93.30 ± 13.03 mmHg, and 52.79 ± 15.49 mmHg, respectively (Table 2).

3.2. Associations of O_3 with the prevalence of hypertension and blood pressure

For the long-term effects of O_3 on the prevalence of hypertension, we observed positive associations between hypertension and O_3 in both the crude model and the two adjusted models. In the crude model, each 10 μg/m^3 increase in long-term O_3 exposure was associated with a 13.6% (95% CI: 5.2%, 22.6%) increase in the prevalence of hypertension. After adjusting for temperature, humidity, age, gender, and residence (Adjusted Model 1), O_3 exposure was significantly associated with the prevalence of hypertension (percentage change = 13.9%, 95% CI: 4.7%, 23.8%). When additionally adjusted for marital status, smoking status, and drinking status (Adjusted Model 2), long-term exposure to O_3 still had a positive and significant association with the prevalence of hypertension (percentage change = 13.7%, 95% CI:4.8%, 23.3%). (Fig. 2).

The association between long-term exposure to O_3 and blood pressure is summarized in Fig. 2. In the crude model, we found that a 10 μg/m^3 increase in 3-year O_3 exposure was associated with 1.024 mmHg (95% CI: 0.174, 1.875), 0.627 mmHg (95% CI: 0.174, 1.875), and 0.754 mmHg (95% CI: 0.214, 1.294) increases in SBP, DBP, and MAP, respectively. After being partly-adjusted and fully-adjusted for potential confounders, positive and significant associations were still observed in association of O_3 exposure with SBP, DBP, and MAP. In the fully-adjusted model (Adjusted Model 2), each 10 μg/m^3 increase in O_3 exposure was associated with 1.128 mmHg (95% CI: 0.248, 2.005), 0.679 mmHg (95% CI: 0.059, 1.298), and 0.820 mmHg (95% CI: 0.245, 1.358) increases, respectively. No significant associations were observed

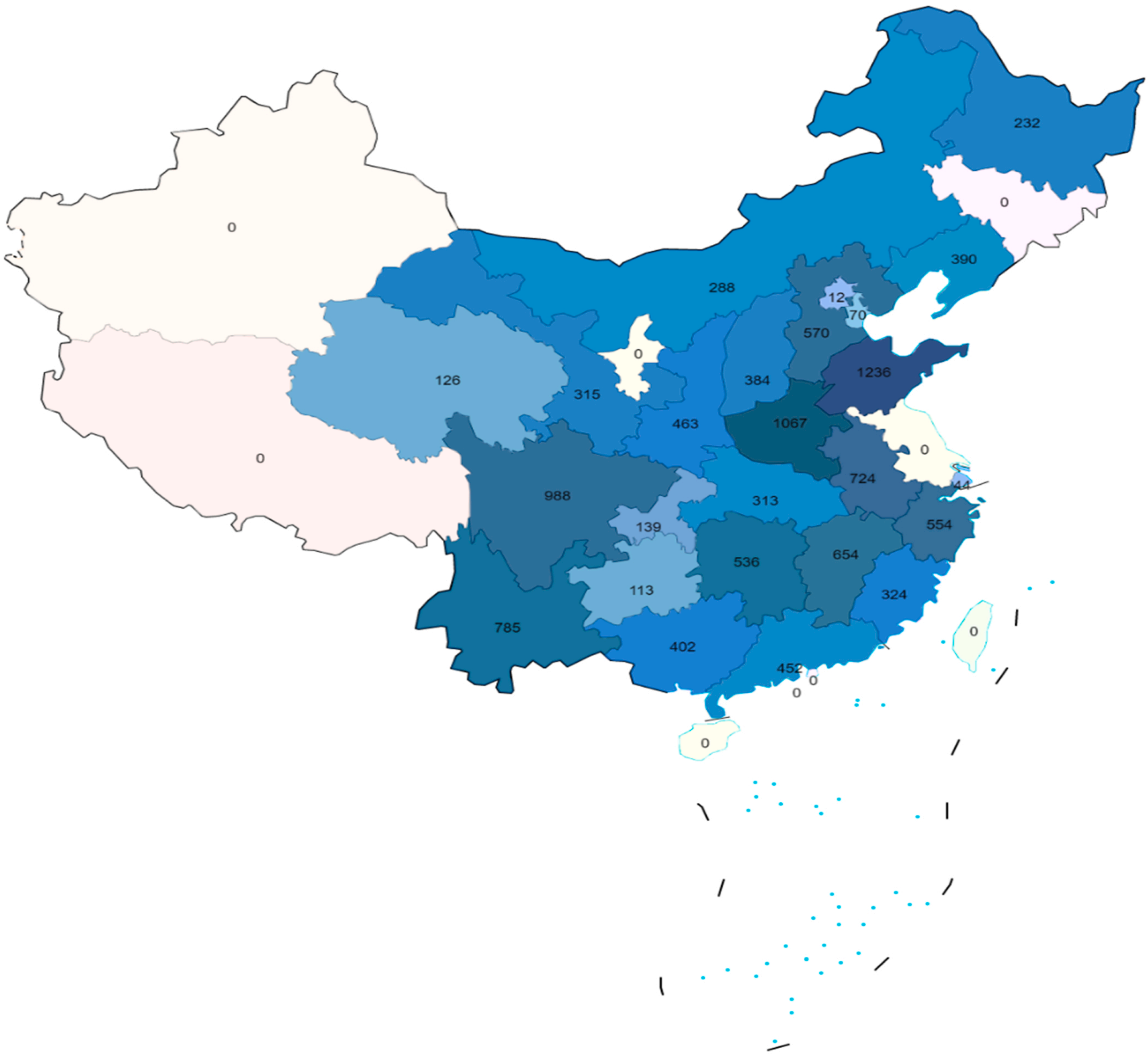

Fig. 1. The geographical distribution of 12,028 middle-aged and older adults from 27 provinces in China. The geographical distribution was graphed in the Standard Mapping service of the Ministry of Natural Resources of China (http :// bzdt.ch.mnr.gov.cn/).

in the crude model or the two adjusted models between O_3 exposure and PP (Fig. 2).

3.3. Associations between O_3 and BMI, and the mediation effects of BMI in the association of O_3-hypertension and O_3-blood pressure

We firstly explored the associations between O_3 exposure and BMI, and found positive and significant associations in all three models (Fig. 2). In the adjusted model 2, each 10 μg/m^3 increase in long-term exposure to O_3 was associated with a 0.357 kg/m^2 (95% CI: 0.206, 0.507) increase in BMI. We then employed mediation analysis to examine the mediation effects of BMI in the association of O_3-hypertension and O_3-blood pressure. Results showed that BMI appeared to have significant mediation effects in all three models for hypertension, SBP, DBP, and MAP. In adjusted model 2, BMI mediated 40.08%, 37.25%, 39.95%, and 33.51% of the effects of long-term exposure to O_3 on hypertension, SBP, DBP, and MAP, respectively (Fig. 3, Table S1). No significant associations of O_3-BMI or mediation effects of BMI in the associations of O_3-PP were found in the crude model or the two adjusted models.

3.4. Subgroup analysis

We also conducted several subgroup analyses to assess the effects among participants with different characteristics (Fig. 4; Table S2). While no significant association was observed in the association between O_3 and PP, we discovered positive and significant associations among elderly adults. Each 10 μg/m^3 increase in O_3 exposure was associated with a 1.321 mmHg (95% CI: 0.381, 2.259) increase in PP. Moreover, we also observed that participants with a single, divorced, or widowed marital status, and those that drink alcohol more than once a month were more sensitive to O_3 exposure, even if the *P*-interaction was insignificant. Besides, the geographical area was also found to be an effective modifier in the associations of O_3 exposure with hypertension,

Table 1
Basic characteristics of the participants.

Characteristics[a]	Total (n = 12028)	Non-Hypertension (n = 7442)	Hypertension (n = 4586)	*P* value[b]
Age, years	60.66 ± 9.68	59.09 ± 9.30	63.23 ± 9.74	< 0.001
BMI, kg/m^2	23.87 ± 3.65	23.34 ± 3.49	24.75 ± 3.73	< 0.001
Age Group				< 0.001
Elderly (≥ 65 years)	4059 (33.75)	2034(27.33)	2025(44.16)	
Middle-aged < 65 years)	7969 (66.25)	5408(72.67)	2561(55.84)	
BMI Group				< 0.001
< 25 kg/m^2	7748 (64.42)	5277(70.91)	2471(53.88)	
≥ 25 kg/m^2	4280 (35.58)	2165(29.09)	2115(46.12)	
Gender				0.043
Male	7442 (61.87)	3429 (46.08)	2200 (47.97)	
Female	4586 (38.13)	4013 (53.92)	2386 (52.03)	
Residence				
Rural	7495 (62.31)	4965 (66.72)	3363 (73.33)	0.011
Urban	4533 (37.69)	4027 (54.11)	1623 (35.39)	
Marital status				
Married and living with a spouse	9924 (82.51)	6265 (84.18)	3659 (79.79)	< 0.001
Married but living without a spouse	499 (4.15)	335 (4.50)	164 (3.58)	
Single, divorced, and windowed	1604 (13.34)	842 (11.31)	762 (16.62)	
Smoking Status[c]				
Non-smoker	6846 (56.92)	4297 (57.74)	2549 (55.58)	0.005
Smoker	767 (6.38)	494 (6.64)	273 (5.95)	
Drinking Status[c]				< 0.001
Non-drinker	7782 (64.70)	4767 (64.06)	3015 (65.74)	
Drink but less than once a month	1056 (8.78)	71 3(9.58)	343 (7.48)	
Drink more than once a month	3175 (26.40)	1958 (26.31)	1217 (26.54)	

[a] For continuous variables, numbers represent the mean ± standard deviation and for categorical variables, numbers represent count (percentage).
[b] *P* value for significance test between non-hypertension participants and hypertension participants. Abbreviations: BMI, Body mass index.
[c] For variables, missing values existed.

SBP, and MAP, with greater effect estimates in those participants from the northern area (*P*-interaction < 0.05).

3.5. Sensitivity analysis

Except for the association between 2-year O_3 exposure and SBP in the main effects model, the associations of O3 with blood pressure were consistent in terms of sensitivity, particularly when participants taking anti-hypertensive drugs or participants changing their residential addresses were excluded, and when 2-year and 1-year O_3 exposure were applied (Table S3-S6). The 4-way decomposition median analysis suggested that both reference interactions (effects due to interaction only) and mediated interactions (effects due to mediation and interaction) were not statistically significant (except for the mediated interaction of BMI and SBP, PP). However, the results of pure indirect effect (effects due to mediation only) were all significant (SBP, DBP, MAP, PP and Hypertension, all $P < 0.001$), which suggested that BMI might mainly play a mediated effect in O_3-induced blood pressure change and hypertension (Table S7).

Table 2
Descriptive statistics of the 3-year average levels of O_3, temperature, humidity, and blood pressure.

	Mean	SD	P25	P50	P75	IQR
Air pollution						
O_3 (μg/m^3)	84.22	7.19	79.05	82.82	88.56	9.51
Temperature and humidity						
Temperature (℃)	24.00	15.57	14.10	16.00	72.00	57.90
Humidity (%)	69.43	9.62	63.00	72.00	77.00	14.00
Blood pressure						
SBP (mmHg)	128.50	19.90	114.33	126.33	141.00	26.67
DBP (mmHg)	75.71	11.68	67.67	74.67	82.67	15.00
MAP (mmHg)	93.30	13.03	83.89	92.33	101.56	17.67
PP (mmHg)	52.79	15.49	43.00	50.33	60.67	17.67

Abbreviations: O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SD, standard deviation; P25, P50, P75, Lower, median and upper quartiles of variables; IQR, interquartile range.

4. Discussion

In this national cross-sectional study of 12,208 Chinese middle-aged and older adults, long-term exposure to O_3 was significantly associated with an increase in the prevalence of hypertension, SBP, DBP, and MAP levels. Consistent with our hypotheses, this study demonstrated a significant increase in BMI in response to long-term O_3 exposure and further suggested that BMI might play a crucial mediation effect in O_3-induced hypertension and blood pressure (SBP, DBP, and MAP) increase. To the best of our knowledge, this was the first study to assess the mediation effect of BMI in the associations of O_3 with hypertension and blood pressure.

Previous epidemiological studies have evaluated the long-term effects of O_3 on hypertension and blood pressure (Dong et al., 2013; Weaver et al., 2021; Yang et al., 2019b, 2018). For example, Yang et.al. performed a meta-analysis of the associations of air pollution with hypertension and blood pressure in 2018. They found no significant association between long-term exposure to O_3 and blood pressure (SBP and DBP) and associations of O_3 with hypertension were not meta-analyzed because only two studies had been published. The lack of significant associations observed in Yang's study might have been caused by the limited number of included studies (only four studies). Apart from the meta-analysis mentioned above, several studies published recently reported positive and significant effects of long-term exposure to O_3 on hypertension and blood pressure. For example, Yang et.al. investigated 15,477 adults from three cities in northeastern China and found each 10 μg/m^3 increase in O_3 was associated with a 5% (odds ratio (OR) = 1.05; 95% CI: 1.00, 1.12) increase in the prevalence of hypertension (Yang et al., 2019b), which was similar to our results. As for blood pressure, an African American cohort study also reported positive associations between long-term exposure to O_3 and blood pressure. They found that each 10 μg/m^3 increase in O_3 exposure was associated with a 0.67 mmHg (95% CI: 0.27, 1.06), 0.42 mmHg (95% CI: 0.20, 0.63), and 0.50 mmHg (95% CI: 0.26, 0.74) increase in SBP, DBP and MAP, respectively (Weaver et al., 2021). By comparison, these published studies agreed in principle but not in detail. These differences might have resulted from the different populations, study regions, and number of participants in the studies. Moreover, we noticed that the estimated effects of our study were slightly higher than those of the two studies above, which might be mainly attributed to the higher susceptibility to cardiovascular diseases in the middle-aged and older populations. Overall, this nationally representative study of middle-aged and older Chinese people suggested that long-term exposure to O_3 could

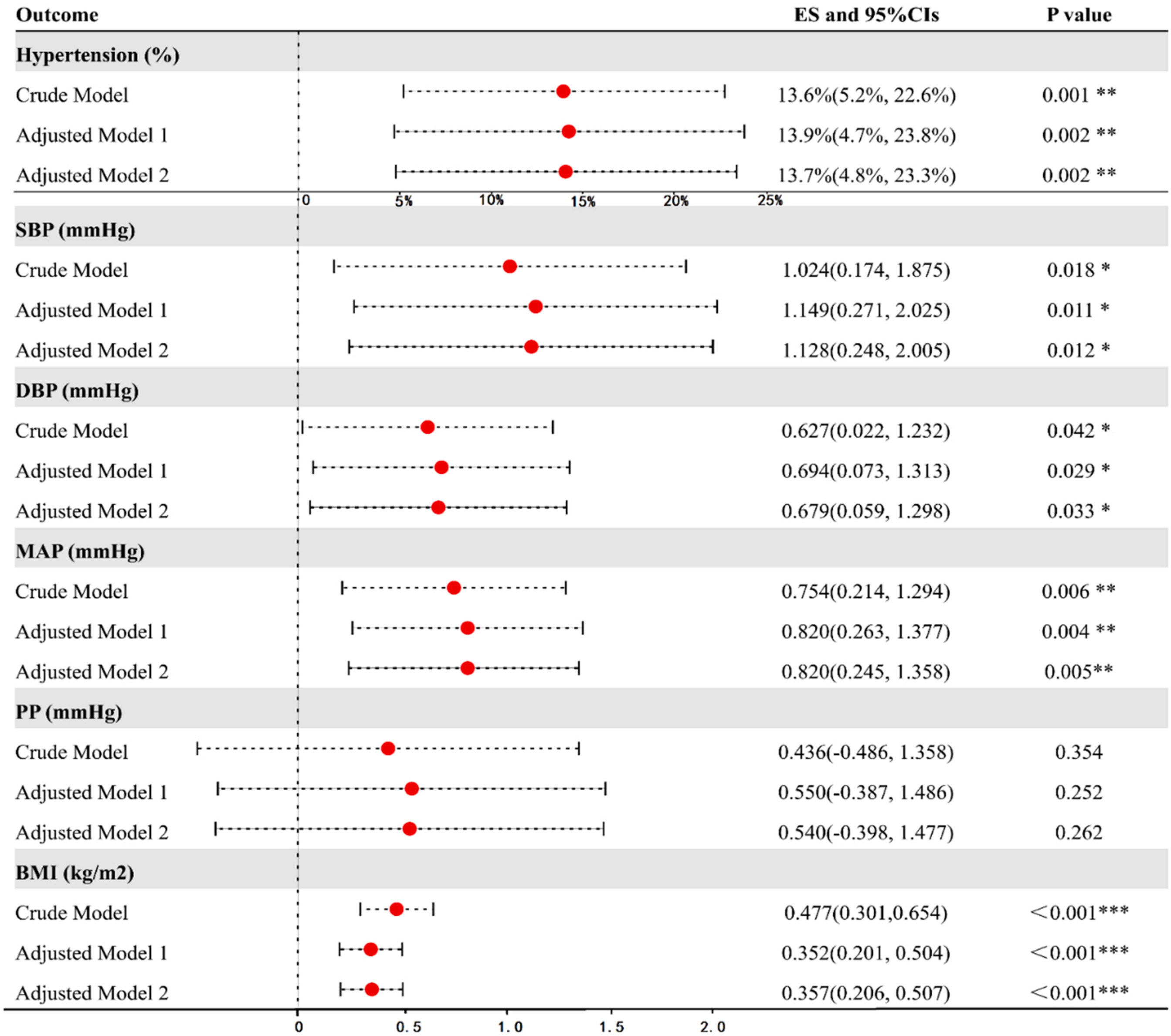

Fig. 2. Percentage changes of in the prevalence of hypertension, blood pressure changes, and body mass index changes associated with per 10 μg/m^3 increment in long-term exposure to O_3. Notes: Crude model, no adjustment; Adjusted model 1, adjusted for temperature, humidity, age, gender, and dwelling type; Adjusted model 2, adjusted for temperature, humidity, age, gender, residence, marital status, smoking status, and drinking status; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
Abbreviations: O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; BMI, Body mass index.

lead to increased hypertension risk and higher blood pressure, which provided additional epidemiological evidence of the adverse effects of O_3 on the cardiovascular systems.

Our study showed that BMI mediated 40.08%, 37.25%, 39.95%, and 33.51% of the effects among the associations of long-term exposure to O_3 with hypertension, SBP, DBP, and MAP, respectively. Despite the fact that no similar study employing a mediation effect model has been published, we noticed that some studies could support our findings to some extent. Firstly, several studies have examined the association between O_3 and BMI (Huang et al., 2020; Kim et al., 2019; Yang et al., 2019c) and the effects of BMI on hypertension and/or blood pressure (Chen et al., 2015; Fedecostante et al., 2015; Liu et al., 2019c; Sagaro et al., 2021). For example, a meta-analysis found that each 10 μg/m^3 increase in long-term exposure to O_3 was associated with a 0.21 kg/m^2 (95% CI: 0.17, 0.24) increase in BMI (Huang et al., 2020). A longitudinal study suggested that BMI correlated positively with both SBP (r = 0.336, $P < 0.001$) and DBP (r = 0.334, $P < 0.001$), and overweight and obese participants tended to have higher risk of pre-hypertension and hypertension than those with a normal weight (Sagaro et al., 2021). Secondly, several studies have examined the interaction effects of BMI in the associations of O_3 with hypertension and/or blood pressure (Dong et al., 2015; Xing et al., 2020; Yang et al., 2019b; Zhao et al., 2013). A large cross-sectional study of 33 Chinese Communities indicated that the long-term effects of O_3 on hypertension and blood pressure (SBP, DBP) were consistently stronger among overweight/obese participants than normal-weight participants (Zhao et al., 2013). For example, they found that each 22 μg/m^3 increase in O_3 exposure was associated with a 5% (OR = 1.05; 95% CI: 0.99, 1.13) increase of hypertension in normal-weight participants, and a 19% (OR = 1.19; 95% CI: 1.10, 1.28) and 24% (OR = 1.24; 95% CI:1.03, 1.49) increased hypertension risk in overweight and obesity adults, respectively, with significant interactions ($P < 0.001$).

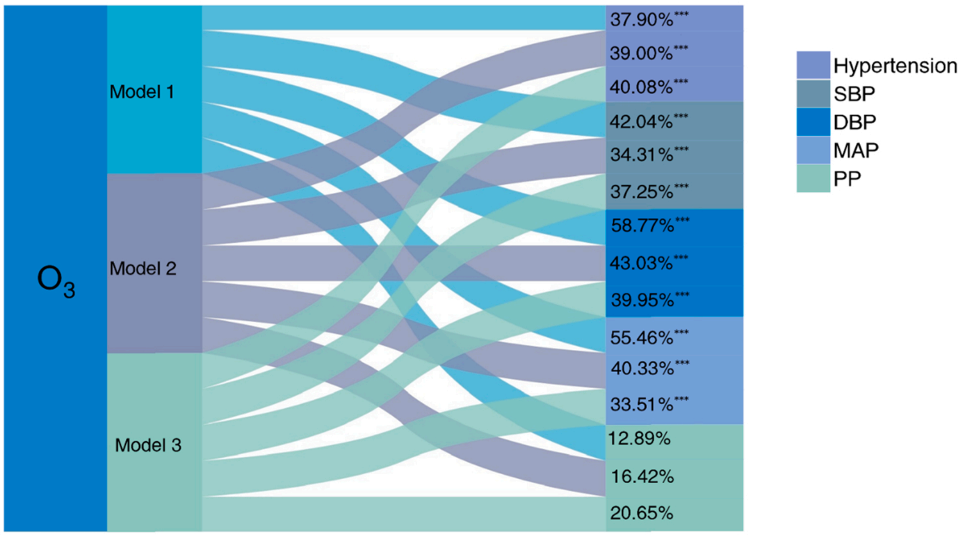

Fig. 3. The mediation proportions (%) by body mass index (BMI) in the association between O_3 and hypertension, and O_3 and blood pressure. Notes: Model 1, crude model, no adjustment; Model 2, adjusted model 1, adjusted for temperature, humidity, age, gender, and dwelling type; Model 3, adjusted model 2, adjusted for temperature, humidity, age, gender, dwelling type, marital status, smoking status, and drinking status; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Results were shown the mediation proportions (%) by Body mass index (BMI) in the association between O_3 and hypertension, and blood pressure. For example, 37.90% of the mediation proportion suggested that BMI was responsible for 37.90% of the mediation effects in the O_3-induced hypertension risk increase in Model 1. Abbreviations: O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

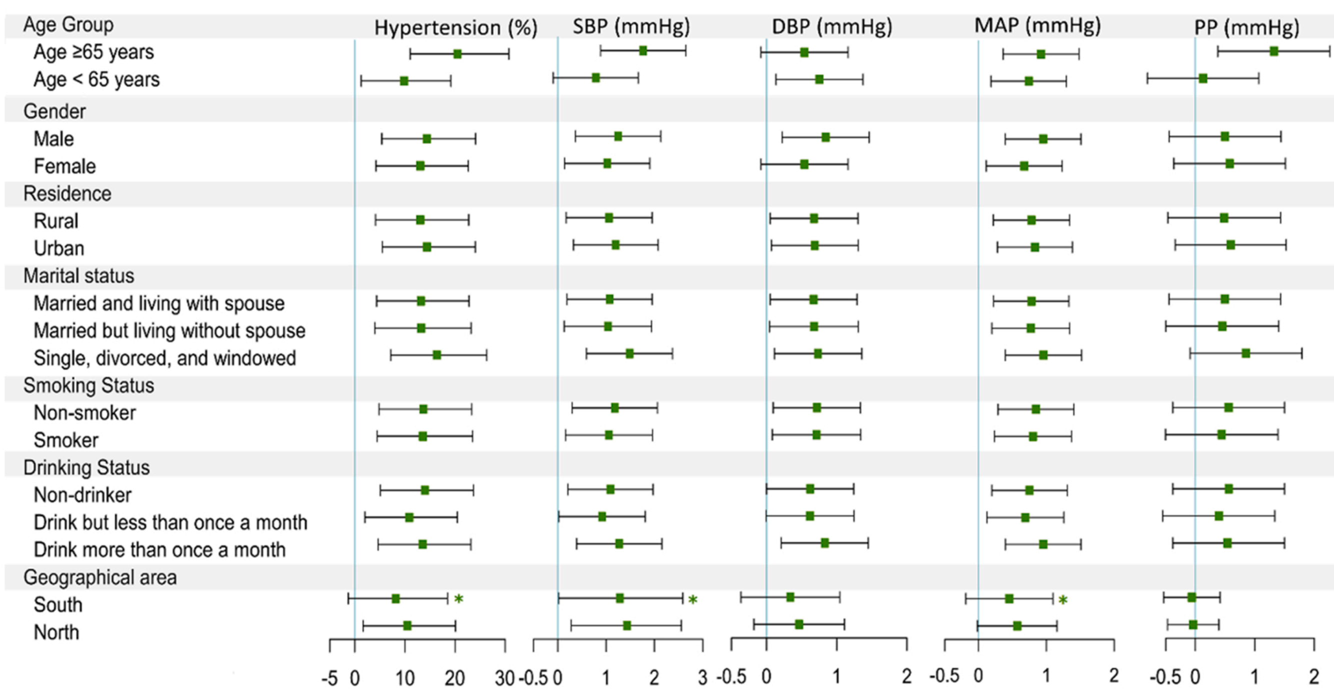

Fig. 4. Subgroup analysis by age, gender, residence, marital status, smoking, and drinking status for the associations between the prevalence of hypertension, blood pressure, and long-term exposure to O_3. Notes: Marital 1, Married and living with a spouse; Marital 2, Married but living without a spouse; Marital 3, Single, divorced, and windowed; Drink 1, Drink but less than once a month; Drink 2, Drink more than once a month. Results were shown in the percentage changes (%) of hypertension, blood pressure changes(mmHg) associated with per 10 μg/m^3 increment in long-term exposure to O_3. Abbreviations: O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. * *P-interaction* < 0.05; ** *P-interaction* < 0.01; *** *P-interaction* < 0.001.

The mechanism of the mediation effects of BMI in O_3-induced hypertension and increased blood pressure is unclear. The possible explanations are insulin resistance (IR), dysfunction of the renin-angiotensin-aldosterone system (RAAS), and sympathetic nervous system (SNS). In brief, exposure to ambient O_3 could induce a series of systematic inflammation and oxidative stress reactions (Day et al., 2017; Xia et al., 2018). Those reactions may further cause a lipid metabolism disorder (Kim et al., 2019) and endothelial dysfunction (Rich et al., 2018), eventually leading to elevated BMI levels. Furthermore, people with high BMI levels (such as those who are overweight and obese) are more likely to contribute to IR, dysfunction of the RAAS and SNS systems (Kurukulasuriya et al., 2011), and structural and functional kidney changes (Sharma, 2004), leading to hypertension and elevated blood pressure (DeMarco et al., 2014).

Several limitations should be mentioned. Firstly, the primary limitation of this study was its cross-sectional design. The cause-and-effect of the association of O_3 exposure with blood pressure and hypertension and its mediation effect of BMI cannot be inferred in this study, thus, the longitudinal studies are needed to confirm our results, especially the mediation effects of BMI. Secondly, some of our participants with hypertension were obtained from self-reported medical history and medication history, thus recall bias (Li et al., 2019) and reporting bias

(Berete et al., 2021) might exist, and the anti-hypertensive medication use of several participants would also influence their blood pressure. However, the sensitivity analysis of excluding anti-hypertensive medication users suggested that the association of O_3 exposure with blood pressure was robust. Thirdly, the O_3 concentrations of individuals were estimated at county-city levels for the absence of more detailed addresses, thus, there may be some deviation between our estimate and the actual situation. Further studies with more accurate exposure estimations are warranted to confirm our results. Fourthly, multi-pollutant models were not performed because of the high co-linearity that exists among O_3 and other air pollutants (Li et al., 2020). Finally, salt intake and other lifestyle characteristics were not available in CHARLS, which might induce blood pressure and hypertension risk changes (Li et al., 2020; Neal et al., 2021), However, those confounders could be partly adjusted by including a random effect term of community ID in the statistical models. Further studies including the control of more confounders are urgently warranted to confirm our results.

5. Conclusions

In summary, our study suggested that long-term exposure to O_3 was positively associated with the prevalence of hypertension and blood pressure levels. BMI plays a crucial mediation effect in O_3-induced hypertension and blood pressure increase. Given the rapidly aging society, severe O_3 pollution, and heavy cardiovascular disease burden, our findings provide epidemiological evidence for the prevention of cardiovascular risks and key populations related to long-term exposure to O_3.

CRediT authorship contribution statement

Conceptualization: ZP N, ZZ D, XJ Y; Data curation: ZP N, ZZ D, J W; Formal analysis: ZP N, ZZ D; Funding acquisition: WJ Q, XJ Y; Investigation: ZP N, ZZ D, DH H, KY Z, YM J; Methodology: ZP N, ZZ D, J W; Project administration: WJ Q, XJ Y; Resources: WJ Q, XJ Y; Software: ZP N, ZZ D; Supervision: DH H, KY Z, YM J; Validation: KY Z, FL W, WH W; Visualization: KY Z, FL W, WH W; Roles/Writing – original draft: ZP N, ZZ D; Writing – review & editing: FL W, WH W, WJ Q, XJ Y.

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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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.113901.

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