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Long-term exposure to ambient ozone and cardiovascular diseases: Evidence from two national cohort studies in China

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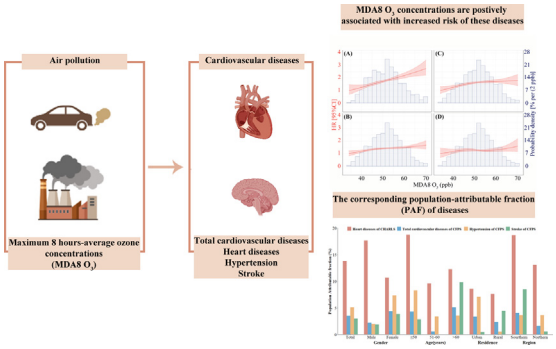
HIGHLIGHTS

- First cohort study in China to investigate long-term ambient O_3 exposure and CVD.
- MDA8 O_3 may increase the risk of total CVD, heart disease and hypertension.
- Effects of MDA8 O_3 were greater in males, urban areas, and Southern China.
- We also provided the PAFs of CVD attributable to MDA8 O_3.
- This study extended our understanding of chronic health effects of ambient O_3.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: The health effects of ambient ozone have been investigated in many previous studies. However, the effects of long-term exposure to ambient ozone on the incidence of cardiovascular disease (CVD) remain inconclusive.
Objectives: To estimate the associations of long-term exposure to maximum daily 8-hours average ozone (MDA8 O_3) with the incidence of total CVD, heart disease, hypertension, and stroke.
Methods: This was a prospective cohort study, and the data was obtained from the China Health and Retirement Longitudinal Survey (CHARLS) implemented during 2011–2018 and the China Family Panel Studies (CFPS) implemented during 2010–2018. We applied a Cox proportional hazards regression model to evaluate the associations of MDA8 O_3 with total CVD, heart disease, hypertension, and stroke risks, and the corresponding population-attributable fractions (PAF) attributable to MDA8 O_3 were also calculated. All analyses were conducted by R software.
Results: The mean MDA8 O_3 concertation of all included participants in the CHARLS and CFPS were 51.03 part per billion (ppb) and 51.15 ppb, respectively. In the CHARLS including 18,177 participants, each 10 ppb increment in MDA8 O_3 concentration was associated with a 31% increase [hazard ratio (HR)

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= 1.31, 95% confidence interval (CI): 1.22–1.42] in the risk of incident heart disease, and the corresponding population-attributable fractions (PAF) was 13.79% [10.12%-17.32%]. In the CFPS including 30,226 participants, each 10 ppb increment in MDA8 O_3 concentration was associated with an increase in the risk of incident total CVD (1.07 [1.02–1.13]), and hypertension (1.10 [1.03–1.18]). The PAFs of total CVD, and hypertension attributable to MDA8 O_3 were 3.53% [0.82%-6.16%], and 5.11% [1.73%-8.38%], respectively. Stratified analyses showed greater associations in males, urban areas, and Southern China. *Conclusions:* Long-term exposure to MDA8 O_3 may increase the incidence of CVD. Therefore, the policies that control O_3 and related precursors are persistently needed.

Introduction

Ground ozone (O_3) is an air pollutant primarily produced by photochemical reactions between nitrogen oxides (NOx) and volatile organic compounds (VOCs) [1]. Combined with the global warming, the rapid industrialization and urbanization worldwide has substantially increased the global ambient O_3 concentration [2]. The Global Burden of Disease (GBD) 2019 reported that 365 thousand deaths were attributed to ambient O_3 worldwide in 2019, and the attributable deaths in China was 93.2 thousand [3].

China is one of the most populous counties where air pollution is a serious public health challenge [4]. There are many new technologies emerging to prevent and control air pollution, such as many newly synthesized nanomaterials that can act as photocatalysts to reduce the negative environmental impact of pollutants [5,6]. To combat the severe air pollution, the Chinese governments have also established a succession of stringent policies and measures, which has successfully controlled most air pollutants particularly fine particulate matter [7,8]. However, these policies inappropriate reduced NOx rather than VOCs leading an increase in the ambient O_3. The national population-weighted mean concentrations of maximum daily 8-hours average ozone (MDA8 O_3) has risen from 89.34 $\mu g/m^3$ in 2013 to 100.96 $\mu g/m^3$ in 2019 [9]. In most cities across China, ambient O_3 has replaced $PM_{2.5}$ as the predominant air pollutant. Furthermore, the ambient O_3 concentration in China is expected to rise between 2019 and 2050 [10].

The GBD 2015 study reported that the global population-weighted O_3 levels increased by 7.2% from 56.8 part per billion (ppb) in 1990 to 60.9 ppb in 2015, with greater increases in O_3 concentration were greater in more populous counties [11]. However, the GBD studies did not include the O_3-related burden of CVD [3]. The associations of long-term exposure to ambient O_3 with cardiovascular effects have been investigated in many previous studies. However, most studies aimed to investigate the long-term influence of O_3 on mortality from CVD [3,12,13]. Very limited studies have attempted to evaluate the effects of long-term O_3 exposure on the incidence of CVD, and their results were inconsistent [14,15]. Moreover, all these previous studies were implemented in high-income countries such as United States, Canada, without evidence from low and middle income (LMI) countries which have different O_3 concentration levels [16].

The U.S. Environmental Protection Agency (EPA) found that the evidence of causal association between long-term O_3 exposure and cardiovascular effects is only suggestive [17]. However, laboratory studies have illustrated that exposure to O_3 results in changes in markers of fibrinolytic, oxidative stress, and inflammatory pathways [18,19,20], which were closely related to the development of CVD. These findings suggested a causal relationship between O_3 exposure and CVD, but more epidemiological studies are needed to clarify the causal relationship. Further, there is still lack of standard for long-term exposure to ambient O_3. Therefore, we believe additional studies are needed.

To fill the above gaps, we conducted an analysis with two national prospective cohorts in China to estimate the associations of long-term O_3 exposure with the incidence of CVD, calculate the O_3-related burden of cardiovascular morbidity, and further explore potential effect modifications.

Materials and methods

Study population and design

The data used in this study was provided by the China Health and Retirement Longitudinal Survey (CHARLS) and China Family Panel Studies (CFPS). The CHARLS study recruited participants aged 45 years or over, as well as her or his spouse, from 450 rural areas and urban communities dispersed throughout 30 provinces across China (Figure S1) [21]. Initially, 17,708 participants were enrolled in the baseline investigation between 2011 and 2012. In 2013, 2015, and 2018, face-to-face computer-assisted personal interviews (CAPI) were applied to follow up all study participants. In each follow-up investigation, new participants were recruited to increase the sample size. There were 25,533 participants in CHARLS study as of the most recent study. However, 7,349 participants were eliminated due to lost to follow-up (n = 2,448), new participants in the latest interview (n = 601), under 45 years old (n = 1,410), CVD patients at baseline (n = 2,332) and lack of key information (n = 565). The detailed information is shown in supplementary materials (Figure S2).

The CFPS study, a large-scale and comprehensive survey, was carried out by the China Social Science Survey Center (ISSS) of Peking University [22,23]. The CFPS was launched during 2010–2011 and included 14,960 households covering 25 provinces of China (Figure S3). All adults aged 18 years or over were included. Using a questionnaire, the CFPS collected household level and individual level information on various aspects including economic status, educational background, physical, and mental health, etc. These participants were followed up in 2012, 2014, 2016, and 2018, respectively. However, 21,848 participants were excluded due to remove core members (n = 179), lack of address information (n = 18,379), and lost to follow-up (n = 3,290). Supplementary materials contain more detailed information (Figure S4).

To examine the associations of long-term MDA8 O_3 exposure with the incidence of CVD, we envisioned a longitudinal cohort design using the CHARLS' 2011 baseline data and data from follow-up in 2013, 2015, and 2018, and the CFPS' 2010 baseline data and data from follow-up in 2012, 2014, 2016, and 2018.

Ethics statement

The CHARLS study involving human participants was ethically reviewed and approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). The CFPS study involving human participants was ethically reviewed and approved by the ISSS of Peking University (IRB00001052-14010).

All subjects in both cohort studies provided their informed consent.

Main measurement outcomes

Participants were defined as having hypertension, heart disease, and stroke if they reported these diseases diagnosed by a doctor. In the CHARLS cohort, heart diseases included coronary heart disease, heart failure, heart attack, angina, or other heart-related problems [24,25]. In the CFPS cohort study, we selected three events as the outcomes: hypertension, total CVD, and stroke including cerebral thrombosis, cerebral infarction, and other cerebrovascular diseases [26]. According to the Disease Classification Codebook and Text Coding Technical Report for CFPS, total CVD in this study included the following diseases: acute rheumatic fever, chronic rheumatic heart disease, angina pectoris, acute myocardial infarction, other ischemic heart disease, pulmonary heart disease, other types of heart disease, hypertensive disease, cerebrovascular disease, and other circulatory diseases [27].

Exposure assessment to air pollution and temperature

Annual data of the highest seasonal [six-month] average of MDA8 O_3 (in parts per billion [ppb]) was obtained from the GBD Study 2019 project, in which the measurements data were obtained from the Tropospheric Ozone Assessment Report (TOAR) and the China National Environmental Monitoring Center (CNEMC) Network [3]. The MDA8 O_3 data was estimated at a spatial resolution of $0.5°\times0.5°$ by using the chemical transport model and Bayesian maximum entropy, and a NASA G5NR-Chem model was used to decline the spatial resolution to 0.1°.

Due to privacy issues, we did not obtain the residential address of each participant. City-level MDA8 O_3 data was used as a proxy for personal data in the CHARLS study, and county-level MDA8 O_3 data was used in the CFPS study. If no disease developed in the participants throughout follow-up, MDA8 O_3 exposure level for each individual was averaged from enrollment to the end of cohort follow-up. When participants in the study developed disease during the study period, each individual's MDA8 O_3 exposure level was averaged from the time of enrollment to the year of the disease occurred. In addition, for participants without disease onset who changed address or who were lost to follow-up after entry into the cohort, the MDA8 O_3 exposure level was averaged from when they entered the cohort to the final follow-up.

The yearly mean $PM_{2.5}$ data for China from 2010 to 2018 were acquired from the global surface $PM_{2.5}$ dataset (V4.GL.03) which was developed by the Atmospheric Composition Analysis Group [28,29]. The ambient temperature data across China from 2010 to 2018 were obtained from the ERA5 which was the reanalysis of the global climate and atmosphere by the fifth generation European Centre for Medium-Range Weather Forecasts (ECMWF) [30]. The individual assessment methods for $PM_{2.5}$ and temperature were the same as that for MDA8 O_3.

Covariates

The following variables were selected as covariates: age, gender, residence, region, education levels, marital status, smoking status, drinking status, physical activity, body mass index (BMI) and ambient $PM_{2.5}$.

Age was divided into three groups: $\leq$50 years, 51to 60 years, >60 years. Residence was defined as a dichotomous variable indicating urban or rural areas. Region is divided into the south or north by the Qin-Huai line [31]. Educational level refers to the number of years of education. Participants with less than 6 years of education may be those who have not reached the level of elementary school knowledge, those with 7 to 12 years of education may be those who have reached the level of secondary school teaching, and most of those with more than 12 years may have university knowledge. Marital status was divided into three groups, namely unmarried, married and other marital status. Unmarried means that the participants has never been married, and other marital status means that the participants may be divorced, widowed, etc. Current smokers were defined as the participants who smoked more than 100 cigarettes in a lifetime and still smoked now or have smoked cigarettes in the last month [32,33]. Current drinkers were defined as the participants who drink alcohol 3 times a week in the past 1 month or in the past year [34]. Physical activity was defined as a dichotomous variable indicating never or ever [35]. Body mass index (BMI) was generated by dividing weight in kilograms by height in m^2. BMI was divided into three groups: <18.5 kg/m^2, 18.5 to 23.9 kg/m^2 and $\geq$ 24.0 kg/m^2. (Table S1).

Statistical analysis

We adopted a time- dependent Cox proportional hazards regression model to analyze the associations of long-term MDA8 O_3 exposure with total CVD, heart disease, hypertension, and stroke incidence [36]. The statistical analysis is consistent with previous research in which annual concentrations of air pollutants were assigned to each year of follow-up [37]. In comparison to the previous method, which used the average from enrolment to the end of cohort follow-up, this method using time-varying covariates and coefficients in the Cox hazards model would decrease the likelihood of exposure bias during long-term follow-up cohort [38]. The approach applied to evaluate the proportional risk hypothesis was assessed with the weighted Schoenfeld residuals [39], by which no violation was found ($P > 0.05$). The variable of MDA8 O_3 was imputed into the model as a continuous variable. When the linear association was estimated, we presented the hazard ratio (HR) and its 95% confidence interval (CI) for each 10 ppb increment in the MDA8 O_3 concentration. By contrast, when the nonlinear association was estimated, we used a natural spline (ns) function with three degrees of freedom (3*df*s) to examine the nonlinear effects [40].

The method for calculating the population-attributable fractions (PAF) of CVD attributable to MDA8 O_3 has been described and explained in detail in previous articles [41], and has also been well validated in other studies [42].

We also applied several types of subgroup analyses to examine the modification effects of gender, age group, residence, and region. A 2-sample *z* test was used to test the difference in the associations among different subgroups [43].

Sensitivity analyses

By additionally adjustment for ambient temperature, the sensitivity analyses were done to verify the robustness of associations between MDA8 O_3 and CVD.

All above analyses were conducted by R software (V4.1.1, R Development Core Team). All statistical analyses were two-sided, and statistical significance was defined by P-value < 0.05.

Results

General characteristics of study participants

There were 18,177 participants selected from the CHARLS cohort, contributing 101,171 person-years of observation, with an average 5.57 years of follow-up. Out of the total participants,

8,961 (49.3%) were females, 6,110 (33.6%) were aged over 60 years, 10,959 (60.3%) resided in rural areas, 10,644 (58.6%) resided in Southern China, and 2,021 (11.1%) reported new heart disease during the follow-up period (Table 1).

A total of 30,226 individuals were selected from the CFPS cohort, with a total of 213,329 person-years of observation, and an average 7.05 years of follow-up. Of these participants, 15,617 (51.7%) were females, 5,616 (18.6%) were aged over 60 years, 16,966 (56.1%) resided in rural areas, and 13,345 (44.2%) resided in Southern China. During the follow-up, 3,980 (13.2%), 2,335 (7.7%), and 1,122 (3.7%) reported new incidence of CVD, hypertension, and stroke, respectively (Table 1 and Table S2).

The mean MDA8 O_3 concertation of all included participants in the CHARLS and CFPS cohorts were 51.03 ppb and 51.15 ppb, respectively. The mean $PM_{2.5}$ concertation of all included participants in the CHARLS and CFPS cohorts were 46.19 μg/m^3 and 50.33 μg/m^3, respectively. The MDA8 O_3 was positively correlated with ambient $PM_{2.5}$ ($r = 0.50$, $P < 0.001$ in CHARLS, $r = 0.45$, $P < 0.001$ in CFPS), and negatively correlated with ambient temperature ($r = -0.09$, $P < 0.001$ in CHARLS, $r = -0.07$, $P < 0.001$ in CFPS) (Table S3 and Table S4).

Associations of long-term exposure to MDA8 O_3 with incident cardiovascular diseases

We found that the positive nonlinear associations of long-term MDA8 O_3 exposure with incident CVD, particularly for heart disease, and hypertension (Fig. 1). Results of linear analyses also showed positive associations of long-term MDA8 O_3 (per 10 ppb increase) exposure with the risks of incident heart disease (HR = 1.31, [95%CI: 1.22–1.42]), total CVD (1.07, [1.02–1.13]), and hypertension (1.10, [1.03–1.18]) in the total participants.

Stratified analyses showed significant modifications of gender, residence, and region on the effects of MDA8 O_3. For instance, the associations of MDA8 O_3 with incident heart disease were greater in males (1.43 [1.25–1.63]) than in females (1.23 [1.10–1.38]), and in Southern China (1.50 [1.30–1.72]) than in Northern China (1.28 [1.14–1.44]). In addition, the association of MDA8 O_3 with incident hypertension was greater in urban residents (1.15 [1.05–1.26]) than in rural residents (1.01 [0.91–1.12]). We also observed the association of MDA8 O_3 with stroke in Southern China (1.20 [1.02–1.41]) was greater than in Northern China (1.01 [0.90–1.14]). (Fig. 2 and Table S5).

PAFs of CVD attributable to long-term exposure to MDA8 O_3

Fig. 3 shows the PAFs of various CVD attributable to MDA8 O_3. The PAFs of heart disease, total CVD, and hypertension were 13.79% [10.12%-17.32%], 3.53% [0.82%-6.16%], 5.11% [1.73%-8.38%], respectively. Subgroup analyses showed heterogeneous PAFs among various subgroups. For example, the PAF of heart disease were higher in Southern China (18.67% [13.14%–23.85%]), and lower in Northern China (13.09% [7.97%-17.94%]). The PAF of hypertension was greater in urban residents (7.13% [2.47%-11.57%]), and lower in rural residents (0.56% [-4.87%-5.71%]). The PAF of stroke was 9.82% [1.91%-17.11%] in participants aged over than 60 years (Table S6).

Sensitivity analyses

The sensitivity analyses indicated robustness of our results against adjustment for different covariates including ambient $PM_{2.5}$ and temperatures (Table S7).

Table 1
Characteristics of study participants in the CHARLS cohort and CFPS cohort.

Characteristics	CHARLS cohort (n, %)	CFPS cohort (n, %)
All	18,177	30,226
Gender		
Male	9216 (50.7)	14,609 (48.3)
Female	8961 (49.3)	15,617 (51.7)
Age (years)		
Minimum age	45	18
Maximum age	115	92
≤50	5767 (31.7)	18,690 (61.8)
51 ~ 60	6300 (34.7)	5920 (19.6)
>60	6110 (33.6)	5616 (18.6)
Residence		
Rural	10,959 (60.3)	16,966 (56.1)
Urban	7218 (39.7)	13,260 (43.9)
Region		
Southern	10,644 (58.6)	13,345 (44.2)
Northern	7533 (41.4)	16,881 (55.8)
Smoking status		
Current	5827 (32.0)	9310 (30.8)
Former	1522 (8.4)	1844 (6.1)
Never	10,828 (59.6)	19,072 (63.1)
Drinking status		
Current	6713 (36.9)	4850(16.0)
Former	1390 (7.6)	1369(4.5)
Never	10,074 (55.4)	24007(79.4)
Educational level (years)		
≤6	7860 (43.2)	15,913 (52.6)
7 ~ 12	8291 (45.6)	12,410 (41.1)
>12	2026 (11.1)	1903 (6.3)
Marital status		
Unmarried	154 (0.8)	3631 (12.0)
Married	16,209 (89.2)	24,546 (81.2)
Others	1814 (10.0)	2049 (6.8)
Physical activity		
Never	1753 (9.6)	24,792 (82.0)
Ever	16,431 (90.4)	5434 (18.0)
BMI		
Underweight (<18.5 kg/m^2)	1003 (5.5)	3073 (10.2)
Normal weight (18.5 to 23.9 kg/m^2)	10,168 (56.0)	18,525 (61.3)
Overweight (≥24.0 kg/m^2)	7006 (38.5)	8628 (28.5)
Heart disease incidence during follow-up		
NO	16,156 (88.9)	–
Yes	2021 (11.1)	–
Total CVD incidence during follow-up		
NO	–	24,353 (80.6)
Yes	–	3980 (13.2)
Hypertension incidence during follow-up		
NO	–	27,056 (89.5)
Yes	–	2335 (7.7)
Stroke incidence during follow-up		
NO	–	28,781 (95.2)
Yes	–	1122 (3.7)

-: Not available.
Note:
Educational attainment (years) ≤ 6 years means less than 6 years of education.
Educational attainment (years) 7 ~ 12 years means the years of education are greater than or equal to 7 years and less than 12 years.
Educational attainment (years) > 12 years means greater than 12 years of education.
BMI, body-mass index.

Discussion

This study based on two national prospective cohorts across China has estimated the associations of long-term MDA8 O_3 exposure with the incidence of CVD. The results suggest that long-term exposure to MDA8 O_3 had the positively association with the incidence of CVD, particularly for heart disease and hypertension. The effects of MDA8 O_3 were greater in males, urban areas, and Southern China. Quantitatively, 13.79% of heart disease, 3.53% of total CVD, and 5.11% of hypertension may be caused by long-term MDA8 O_3 exposure.

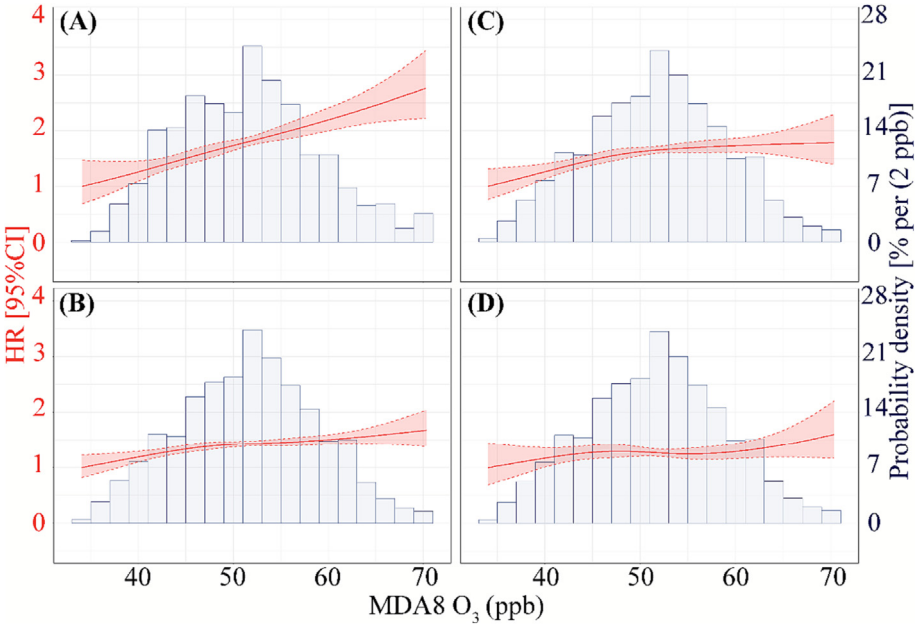

Fig. 1. Exposure-response curves of long-term exposure to MDA8 O_3 concentration with incidence of heart disease (A), total CVD (B), hypertension (C), and stroke (D).

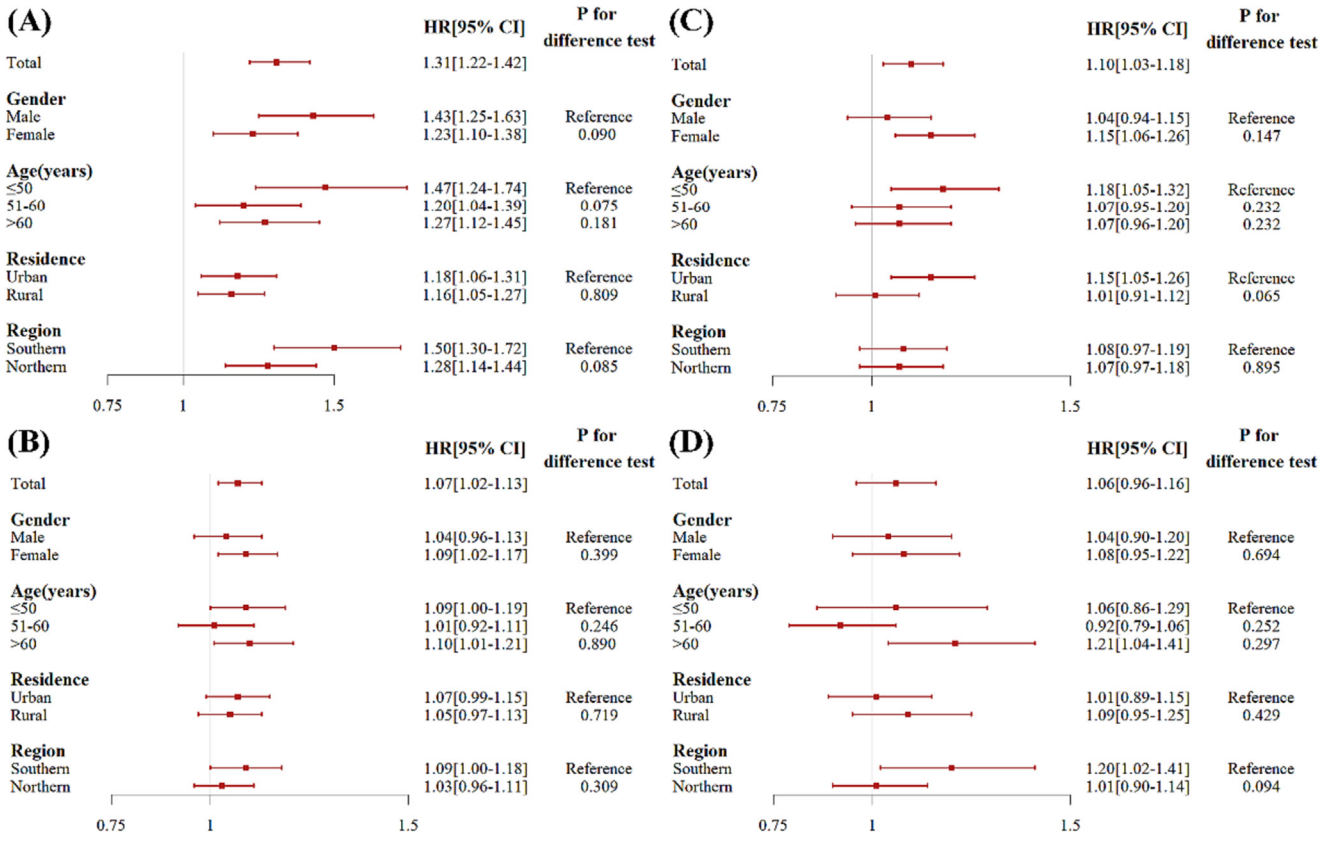

Fig. 2. The hazard ratio (HR, 95%CI) of heart disease (A), total CVD (B), hypertension (C), and stroke incidence (D) for long-term exposure to MDA8 O_3 (per 10 ppb increment). Adjustment for $PM_{2.5}$, age, sex, residence type, region, education level, smoking status, drinking status, physical activity level, marital status and BMI. Abbreviations: HR, hazard ratio; CI, confidence interval.

The 2022 American Heart Association (AHA) Statistical Update states that CVD have posed a significant impacts and disease burden globally [44]. In previous literatures [15,45,46], several investigations have been conducted the impacts of long-term to O_3 exposure on the incidence of CVD, and most of them were implemented in high-income countries. For example, a large cohort study implemented in Canada observed that long-term exposure to O_3 was positively connected with the incidence of congestive heart failure (CHF) and acute myocardial infarction (AMI) [47]. In the Medicare study conducted in USA, Yazdi et al. (2019) observed

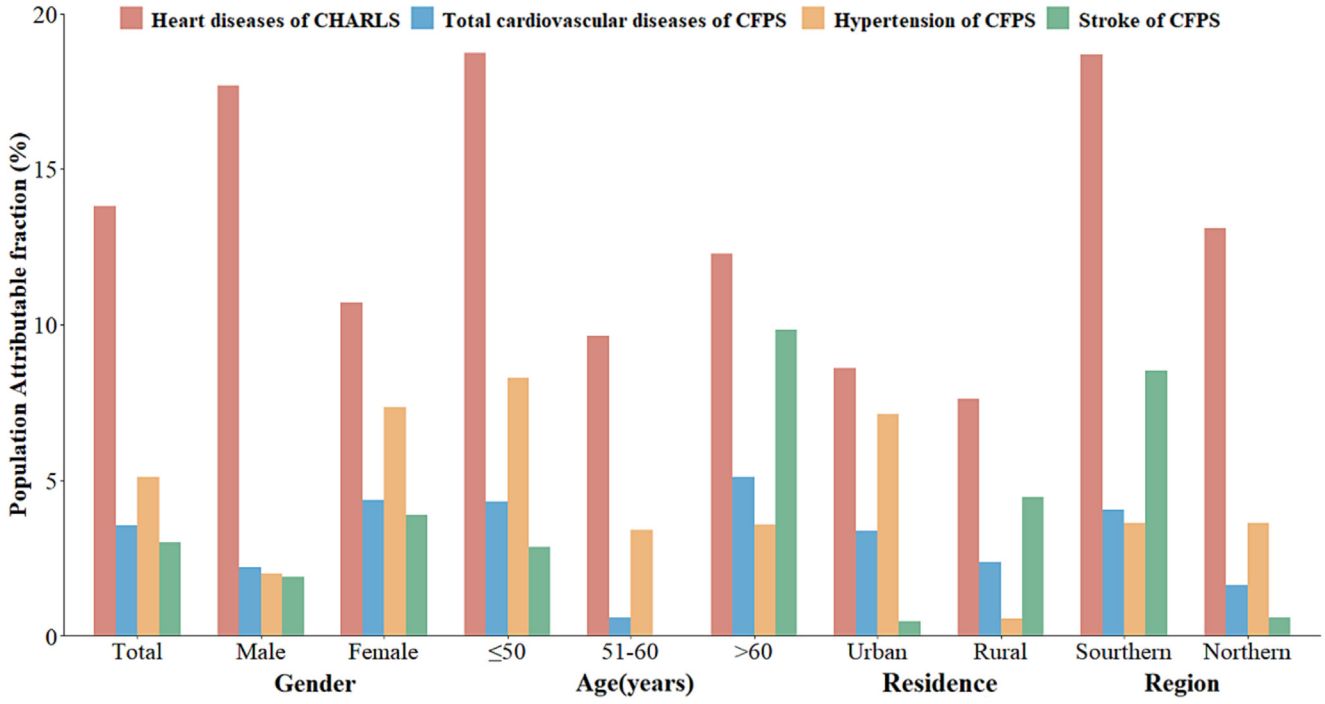

Fig. 3. The population-attributable fraction (PAF) of heart disease, total CVD, hypertension, and stroke for long-term exposure to MDA8 O_3. Note: We estimated only those PAFs of diseases which had positive associations with long-term exposure to MDA8 O_3 in the total participants or various subgroups. Red represents the heart diseases of CHARLS. Blue represents total CVD of CFPS. Yellow represents hypertension of CFPS. Green represents Stroke of CFPS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that long-term O_3 exposure was significantly associated with first hospital admissions for stroke, myocardial infarction (MI), and heart failure [48]. Similarly, our study found that positive associations of long-term exposure to MDA8 O_3 with the incidence of CVD, including heart disease, hypertension. Our findings provide new evidence on the adverse cardiovascular effects of ambient O_3. Table S8 showed the characteristics of previous studies and main findings.

Nevertheless, the long-term effects of ambient O_3 on CVD were inconsistent in existing literature. In a UK cohort study, Atkinson et al. (2013) discovered a null association of long-term O_3 exposure with the incidence of CVD [14]. The 2012 Korean Community Health Survey found that PM_{10}, NO_2, CO, SO_2, and O_3 were not associated with stroke, myocardial infarction, and ischemic heart disease in Korean adults [49]. This disparity may be related to differences in the accuracy of exposure assessment, population characteristics, and O_3 exposure levels [50]. Therefore, we call for more cohort studies to illustrate the impact of chronic exposure to O_3 on cardiovascular health, particularly in LMI countries.

Several plausible biologic mechanisms were proposed in previous studies on the health impacts of O_3 [19,20]. Exposure to O_3, a potent oxidizing gas, may induce oxidative damages to human cells and tissues, which can then lead to immune-inflammatory responses in the lung. For example, exposure to higher O_3 concentration could lead to increased levels of tumor necrosis factor-a (TNF-a), and interleukin-6 (IL-6) in human alveolar macrophages and airway epithelial cells [51]. These immune-inflammatory responses may "spillover" to the circulatory system, and increase the risk of cardiovascular morbidity by affecting hemostasis and autonomic tone [52]. For example, exposure to higher O_3 concentration was associated with an increase in hemostatic markers such as fibrinogen, and von Willebrand factor. O_3 may potentially have effect on the autonomic nervous system, causing adverse cardiovascular effects [52].

We observed a greater association between MDA8 O_3 and incident heart disease in males than in females, which was consistent with previous studies [47]. Compared with female, male have higher frequency and intensity of outdoor activities, and may have more exposure to ambient pollution [53]. Furthermore, the higher prevalence of smoking in males may exacerbate the negative impacts of air pollution on health [54]. It was proposed that the mechanisms of smoking and air pollution on causes of cardiovascular death may be complementary or additive and synergistic [55].

We also observed a stronger association of MDA8 O_3 with CVD in urban population than in rural population. Although we did not find a study that has investigated the urban–rural difference in the long-term association between MDA8 O_3 and CVD, some studies found a stronger effect of other air pollutants on human health in urban area [56,57]. The greater effects of O_3 in urban area may be related to the higher O_3 concentration which was mainly derived from industry and traffic [58]. Higher ambient temperature due to the heat island in urban area may also enhance residential susceptibility to O_3 pollution [59–61]. Moreover, the growing urbanization in China in recent years has contributed to more in-migration of people to urban cities. Since most of these people are likely to live in more polluted areas [62], the damage to their health of air pollution is exacerbated. Hence, more protection measures are needed to protect human health from O_3 pollution in urban areas.

The stratified analyses also showed that the influence of MDA8 O_3 was stronger in Southern China than in Northern China. Such a modification of geographical region on the long-term impact of O_3 on CVD has not been investigated in the literature. However, a national Chinese investigation indicated a stronger link between short-term O_3 exposure and mortality from CVD in Southern China than in Northern China, which supports our findings [63]. This geographical variation could be attributed to the higher ambient temperature in Southern China, which could enhance the health

impact of O_3 [59–61]. In addition, people usually spend more time outdoor in southern region, which may increase their exposure level to O_3 and hence enhance the health impact of O_3 [64]. Our findings suggest that southern residents should take more measures to protect their health, particularly in severer O_3 polluted days. Table S9 showed statistical description of temperature, MDA8 O_3 and age of subjects.

Quantitatively, our results showed that the PAFs of CVD, heart disease, and hypertension caused by long-term exposure to MDA8 O_3 were 3.53%, 13.79%, and 5.11%, respectively. The number of newly diagnosed patients of CVD, heart disease, and hypertension are unknown across China. However, based on the annual average incidence of these three diseases in the present two national cohorts, we estimated that about 1391.58 CVD, 664.31 heart disease, and 764.22 hypertension patients were newly diagnosed in each 100,000 population in China. Out of these new patients, 0.52 million CVD, 0.41 million heart disease, and 0.41 million hypertension patients may be caused by exposure to O_3 across China (Table S10). These figures indicated that the large CVD burden attributable to O_3 in China. Considering this number of CVD patients and the rising of ambient O_3 across China, effective air pollutant control strategies are very necessarily for reducing the cost of CVD.

This study has several strengths. First and foremost, this is a study based on two national cohorts including participants from 30 provinces across China. The large sample size and long follow-up period allowed us to obtain adequate number of new CVD cases, and to confidently estimate their associations with MDA8 O_3 exposure with an ensured statistical power. Second, this is the first cohort study in China to evaluate the relationships between long-term MDA8 O_3 exposure and the incidence of CVD, and explored the modifications. Our findings provided additional information of the adverse health impacts of ambient O_3. Third, detailed individual information was collected in both cohorts, allowing us to adequately control for the potential confounders. Fourth, we also calculated the PAF of MDA8 O_3 exposure, which could be useful in calculating the disease burden of CVD, and has crucial policy implications.

Meanwhile, several limitations should be acknowledged. First, many participants were excluded in the CHARLS and CFPS cohorts, which may result in selection bias (Table S11 and S12). The descriptions of physical activity differ in these two cohorts. The raw data on physical activity in the CHARLS was a continuous variable while the raw data on physical activity in the CFPS was binary. To maintain the consistency of the study, we divided exercise into two categories: Never and ever. In the CHARLS, we performed a sensitivity analysis and discovered that the results did not substantially change using binary variable and continuous variable of physical activity (Table S13). Second, we assessed the O_3 concentration at the city or county level as a proxy of individual exposure, as we had no access to individual residential address due to privacy concerns. We cannot totally exclude the misclassification bias of exposure. In addition, we did not obtain individual information of time-location activity patterns and indoor air pollution, which may also lead to misclassification bias of exposure. However, it was suggested that such misclassification bias is likely to be universal and non-differential [42], and the impacts on our findings may be limited. Third, for noncommunicable chronic diseases such as CVD, there is typically no acute symptom that may be utilized to corroborate the accurate incident data. The diagnosis date is usually utilized as the incident date, which may lead to information bias because the real onset date of CVD may be earlier. Fourth, those CVD patients diagnosed before entering the cohort were excluded in this study. These excluded patients may include most susceptible people who have developed the CVD earlier, which may result in underestimation of O_3 effect.

Although we have collected detailed individual information, the information on industrial exposure and occupational dirtiness indices was not available in CHARLS and CFPS. Some potential confounders were not considered in this study including medication status, comorbidities, dietary habit, physiological and pathological factors and genetic background.

Conclusions

This national cohort study based on CHARLS and CFPS provides new evidence for the more comprehensive study of the association between MDA8 O_3 and the incidence of CVD. Initially, this study strongly suggests the positive association of long-term MDA8 O_3 exposure with the incidence of CVD. The associations were more pronounced in males, Southern China and urban areas. The O_3 exposure may have led to have burden of CVD across China. Our findings combined with previous evidence will aid in establishing a more precise exposure–response function for estimating the disease burden caused by MDA8 O_3. This study extends our understanding of the causal associations between long-term exposure to MDA8 O_3 and CVD. These findings also encourage us to control ambient O_3 pollution to protect public health, with particular attention to vulnerable populations such as men, those living in Southern China, and those in urban areas. Considering the rising of MDA8 O_3 concentration and the incidence of CVD across China, policies that control O_3 and related precursors are persistently needed, particularly in regions with severer O_3 pollution.

Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). The CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (Approval no. IRB00001052-11015) and the CFPS study was approved by the Peking University Biomedical Ethics Review Committee (Approval no. IRB00001052-14010). Informed consent was obtained from all participants in both cohort studies.

CRediT authorship contribution statement

Shuru Liang: Methodology, Formal analysis, Software, Writing – original draft. **Yumeng Chen:** Visualization, Validation, Methodology, Writing – original draft. **Xiaoli Sun:** Conceptualization, Methodology, Software, Writing – original draft. **Xiaomei Dong:** Visualization, Validation, Methodology, Writing – original draft. **Guanhao He:** Data curation, Methodology, Visualization, Validation. **Yudong Pu:** Data curation, Methodology, Visualization, Validation. **Jingjie Fan:** Conceptualization, Visualization, Validation, Writing – review & editing. **Xinqi Zhong:** Methodology, Visualization, Validation, Writing – review & editing. **Zhiqing Chen:** Data curation, Methodology, Visualization, Validation. **Ziqiang Lin:** Visualization, Validation, Methodology, Writing – review & editing. **Wenjun Ma:** Data curation, Methodology, Visualization, Validation. **Tao Liu:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2023.08.010.

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