Environment International 165 (2022) 107280

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Long-term exposure to ozone and cardiovascular mortality in a large Chinese cohort

Shudan Liu [a], Yi Zhang [b], Runmei Ma [b], Xiaofei Liu [a], Jingyuan Liang [a], Hongbo Lin [c], Peng Shen [c], Jingyi Zhang [d], Ping Lu [d], Xun Tang [a], Tiantian Li [b,1,**], Pei Gao [a,e,f,1,*]

[a] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, No. 38 Xueyuan Road, Haidian District, Beijing 100191, China
[b] China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, No. 7 Panjiayuannanli Road, Chaoyang District, Beijing 100021, China
[c] Yinzhou District Centre for Disease Control and Prevention, 1221 Xueshi Road, Ningbo, Zhejiang 315100, China
[d] Wonders Information Co., Ltd, 1518 Lianhang Road, Shanghai, China
[e] Center for Real-World Evidence Evaluation, Peking University Clinical Research Institute, No. 38 Xueyuan Road, Haidian District, Beijing 100191, China
[f] Key Laboratory of Molecular Cardiovascular (Peking University), Ministry of Education, Beijing, China

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Ozone
Long-term exposure
Cardiovascular disease
Mortality
Chinese

ABSTRACT

Background: Evidence for the association between long-term exposure to ozone (O_3) and cause-specific cardiovascular disease (CVD) mortality is inconclusive, and this association has rarely been evaluated at high O_3 concentrations.

Objectives: We aim to evaluate the associations between long-term O_3 exposure and cause-specific CVD mortality in a Chinese population.

Methods: From 2009 to 2018, 744,882 subjects (median follow-up of 7.72 years) were included in the CHinese Electronic health Records Research in Yinzhou (CHERRY) study. The annual average concentrations of O_3 and fine particulate matter ($PM_{2.5}$), which were estimated using grids with a resolution up to 1 × 1 km, were assigned to the community address for each subject. The outcomes were deaths from CVD, ischemic heart disease (IHD), myocardial infarction (MI), stroke, and hemorrhagic/ischemic stroke. Time-varying Cox model adjusted for $PM_{2.5}$ and individual-level covariates was used.

Results: The mean of annual average O_3 concentrations was 68.05 μg/m^3. The adjusted hazard ratio per 10 μg/m^3 O_3 increase was 1.22 (95% confidence interval [CI]: 1.13–1.33) for overall CVD mortality, 1.08 (0.91–1.29) for IHD, 1.21 (0.90–1.63) for MI, 1.28 (1.15–1.43) for overall stroke, 1.39 (1.16–1.67) for hemorrhagic stroke and 1.22 (1.00–1.49) for ischemic stroke, respectively. The study showed that subjects without hypertension had a higher risk for CVD mortality associated with long-term O_3 exposure (1.66 vs. 1.15, $p = 0.01$).

Conclusions: We observed the association between long-term exposure to high O_3 concentrations and cause-specific CVD mortality in China, independent of $PM_{2.5}$ and other CVD risk factors. This suggested an urgent need to control O_3 pollution, especially in developing countries.

Abbreviations: BMI, body mass index; CanCHEC, Canadian Census Health and Environment Cohort; CHERRY, CHinese Electronic health Records Research in Yinzhou; CI, confidence interval; CPS-II, the American Cancer Society Cancer Prevention Study II; CVD, cardiovascular disease; EPA, Environmental Protection Agency; GBD, Global Burden of Diseases; GDP, gross domestic product; HR, hazard ratio; IHD, ischemic heart disease; IQR, inter quartile range; MI, myocardial infarction; O_3, ozone; $PM_{2.5}$, fine particular matter; SD, standard deviation.

* Corresponding authors at: Department of Epidemiology and Biostatistics, School of Public Health, Peking University, No. 38 Xueyuan Road, Haidian District, Beijing 100191, China.
** Corresponding author.
E-mail addresses: litiantian@nieh.chinacdc.cn (T. Li), peigao@bjmu.edu.cn (P. Gao).
[1] Dr. Gao and Dr. Li contributed equally as joint corresponding authors.

https://doi.org/10.1016/j.envint.2022.107280
Received 14 February 2022; Received in revised form 9 April 2022; Accepted 2 May 2022
Available online 17 May 2022

1. Introduction

Ozone (O_3) is a secondary pollutant with strong oxidizing properties (Cakmak et al., 2018). In recent years, the concentrations of other pollutants, such as fine particulate matter ($PM_{2.5}$), have decreased, whereas the ambient O_3 concentration is stable or gradually increasing globally (Global Burden of Diseases [GBD] 2019 Risk Factors Collaborators, 2019; Zhou et al., 2022). Global warming is accelerating because of the rising greenhouse gas emissions and natural climate cycles (Xu et al., 2018), and the associated increase in temperature could further increase the concentrations of O_3 in the future (Likhvar et al., 2015; Pu et al., 2017). A warming climate reduces humidity and wind speed, which decreases the dispersion of nitrogen oxides and volatile organic compounds, in turn prolonging the time available for O_3-forming reactions to occur. Moreover, O_3-forming reactions are enhanced at higher temperatures (Heal et al., 2013; Jhun et al., 2014). In a recent GBD study considering only the effect of O_3 on respiratory disease, the global burden of mortality attributable to ambient O_3 pollution in 2019 increased compared to 1990 (GBD 2019 Risk Factors Collaborators, 2019). Therefore, ambient O_3 pollution is a serious globally public health concern.

Among epidemiological studies, short-term O_3 exposure (from hours to a few days) increases the risk of mortality from respiratory disease, cardiovascular disease (CVD), ischemic heart disease (IHD), and stroke (U.S.EPA, 2020), as well as hospital admissions due to cardiopulmonary disease (Berman et al., 2012; Ensor et al., 2013). However, limited studies have assessed the association between long-term exposure to O_3 and mortality, especially CVD mortality, and the results are inconsistent. As the leading cause of mortality, CVD was responsible for 17.8 million deaths in 2017, accounting for approximately 31.8% of all-cause global deaths (GBD 2017 Causes of Death Collaborators, 2018). Recent large cohort studies in the US and Canada have shown that long-term exposure to O_3 is associated with CVD deaths (Cakmak et al., 2016; Kazemiparkouhi et al., 2020; Lim et al., 2019; Turner et al., 2016; Weichenthal et al., 2017), whereas cohort studies from Denmark (Hvidtfeldt et al., 2019), France (Bentayeb et al., 2015) and the UK (Carey et al., 2013) have reported null or negative associations. Several studies (Lim et al., 2019; Turner et al., 2016; Weichenthal et al., 2017) have suggested the association of O_3 and death from respiratory disease or CVD are in fact non-linear, with a threshold concentration ranging between 25 and 60 $\mu g/m^3$. This may explain the conflict results stated above, because most studies examining the effects of long-term O_3 exposure on CVD mortality were conducted in developed countries where O_3 concentrations are generally below 60 $\mu g/m^3$ (Cakmak et al., 2016; Di et al., 2017; Turner et al., 2016). More significant association may be observed at higher O_3 concentrations that exceed the above-specified threshold range. As well as these inconclusive results, little is currently known about the effect of higher concentrations of O_3. Moreover, as reported by the U.S. Environmental Protection Agency (EPA), the main uncertainty also comes from the limited evidence from epidemiologic studies on the effect of long-term exposure to O_3 on cause-specific CVD outcomes, such as IHD, myocardial infarction (MI) or stroke (U.S.EPA, 2020).

Therefore, by examining O_3 estimates at a high spatiotemporally resolution (up to 1 km grid cells) in a large Chinese cohort study (Lin et al., 2018) of 744,882 adults from 2009 to 2018, with a detailed consideration of $PM_{2.5}$ and individual-level risk factors, we aim to evaluate the associations between long-term exposure to high O_3 concentrations and cause-specific CVD mortality and to examine the concentration–response curves to fill the gap of knowledge about long-term exposure to O_3 related CVD health effects at high O_3 concentrations and to provide epidemiological evidence to support policy making for O_3 control to promote public health.

2. Materials and Methods

2.1. Study population

The CHinese Electronic health Records Research in Yinzhou (CHERRY) study is a large, population-based, observational cohort study integrating individual data within the regional health information system in China. The study is conducted in Yinzhou, Ningbo in Zhejiang Province (29°37′−29°57′ N, 121°08′−121°54′ E), which is located in the coastal area of eastern China, 230 km south of Shanghai, with an area of 1346 km^2 and a total population of 1.24 million in 2016 (Lin et al., 2018). Yinzhou has a subtropical monsoon climate, with mild winters and warm but moist summers. The temperature reaches its highest (32.4 °C; the monthly average high temperature) in July and its lowest (4.0 °C; the monthly average low temperature) in January, with an annual mean temperature of 18.8 °C. Yinzhou typically sees approximately 150.79 mm (5.94 in.) of precipitation and has 168.65 rainy days annually, which mainly occur from June to September.

The protocols of the CHERRY study have been previously described (Lin et al., 2018). In brief, individuals were included if they met all the following inclusion criteria: (1) aged over 18 years on 1 January 2009; (2) had complete information on the date of birth and sex, as well as a valid healthcare identifier; (3) had been living in Yinzhou for at least 6 months and (4) were Chinese nationality (Lin et al., 2018). A total of 1053,565 subjects were included in the original CHERRY cohort study, with registration between January 1, 2009 and December 31, 2017. The registration date of these subjects was used as the baseline date of the study. Subjects with missing addresses at community/village level or missing important information on individual-level risk factors were excluded. The remaining 744,882 subjects from 33 counties (610 communities or villages) were included in the analysis set in this study (Supplementary Figure 1). The baseline characteristics of both the included and excluded participants are summarized in Supplementary Table 1.

2.2. Health data collection

Longitudinal data for subjects are linked through various clinical and administrative databases. The basic demographic information (birth date, sex, education level and residential community or village), lifestyle risk factors (smoking status and alcohol consumption), anthropometric measurements (height and weight), personal medical history (history of hypertension and diabetes mellitus) were collected. Residents were divided into urban and rural according to their addresses, which were categorized from the National Bureau of Statistics. Information on the Gross Domestic Product (GDP) per capita and the accessibility of healthcare facilities were included as the county-level variables. Information on GDP per capita was obtained from Statistical yearbook 2017 in Yinzhou District of Ningbo city, Zhejiang Province in China. Moreover, a score for healthcare accessibility was calculated for each county in Yinzhou District. All public and private hospitals and primary care units within a radius of 3 km of each county were counted. According to the hospital grade (tertiary public hospital or large private hospital, secondary public hospital, or primary care unit), the score of 10, 5 and 2 was assigned to each hospital tertiary, secondary public hospital and primary care unit, respectively. The hospital grade was officially assessed according to the scale of the hospital (number of staffed beds), scientific research, number of doctors, and the level of medical care provided, amongst other factors. The final county-level score was calculated by summing all points from each healthcare units.

2.3. Outcomes

All subjects were followed up until the date of death, moving out of the region, or the end of the study (Dec 31, 2018). Owing to the border adjustment of the Yinzhou district in 2017, follow-up of individuals from

nine counties, who were considered as moving out of the region, were censored on December 31, 2016. As described previously (Lin et al., 2018), vital information (time and cause of death) was collected from January 1, 2009 to December 31, 2018. The death certificates have been reported previously (Wang et al., 2016). The International Statistical Classification of Diseases, 10th Revision, was used to determine the underlying cause of death from CVD (I00-I99), IHD (I20-I25), MI (I21-I22), stroke (I60-I69), hemorrhagic stroke (I61) and ischemic stroke (I63).

2.4. Measurements of air pollutants and other environmental factors

The ground-level daily average concentrations of O_3 and $PM_{2.5}$ in China from 2005 to 2017 were estimated using random forest algorithm at a spatial resolution of 1-km. These estimates have been used previously (Ma et al., 2021a; Zhao et al., 2020) and the modeling methodology has been described in detail elsewhere (Ma et al., 2021b). Briefly, the random forest algorithm considered the important features including ground-based measurements, satellite-based data, outputs from the GEOS-Chem chemical transport model, meteorological variables, land-use terms, road network data, elevation, normalized difference vegetation index and regional and seasonal variables. Original validation data indicated that the model performance was good when comparing model estimates with ground-based measurements, with R^2 value for prediction versus observation for daily average O_3 and $PM_{2.5}$ concentrations of 0.71 and 0.85, respectively. In our study, the primary exposure was annual average O_3 concentrations, which was calculated by averaging the daily average O_3 concentrations over the year. Within our study area, O_3 concentrations were also directly measured from the three monitor stations. The annual average O_3 concentrations from the monitor stations was highly correlated with the model estimate, with an R^2 value of 0.833 (Supplementary Figure 4). In addition, to demonstrate the seasonal fluctuation of O_3 concentration, we provided the directly measured average O_3 levels per month from the included three stations within our study area in the Supplementary Figure 5. As seen from the figure, in our study area, the highest O_3 concentrations are observed in late spring (April - May) and the lowest in winter (November - January). O_3 concentrations remains high from February till October. Therefore, besides the annual average O_3 concentrations, we also provided the analysis based on the warm-season O_3 concentrations (February - October). The temperature and normalized difference vegetation index were also obtained in the form of annual average values. Residential address was available at the communities/villages level in the study. Individuals were classified into 610 communities/villages within the study area. All residents within each community/village were assigned the same exposure estimates. The detailed locations of all communities/villages were marked as green dots in Fig. 1. The latitude and longitude of these community/village-level addresses were determined on an area map using ArcGIS version 10.5. By linking community/village-level addresses to the nearest grids at 1 km resolution, we match the exposures of O_3 and $PM_{2.5}$ to each participant.

2.5. Statistical analysis

The Cox proportional hazards model was used to estimate the association between the annual average O_3 concentrations and cause-specific CVD mortality. To avoid the potential time trend confounding, time-varying O_3 (and $PM_{2.5}$) measurements were used. Individual records during follow-up were split into each calendar year. The corresponding annual average O_3 concentration was assigned to each year as the exposure. Records with follow-up<1 year were kept. The hazard ratio (HR) and 95% confidence interval (Cl) associated with each 10 μg/

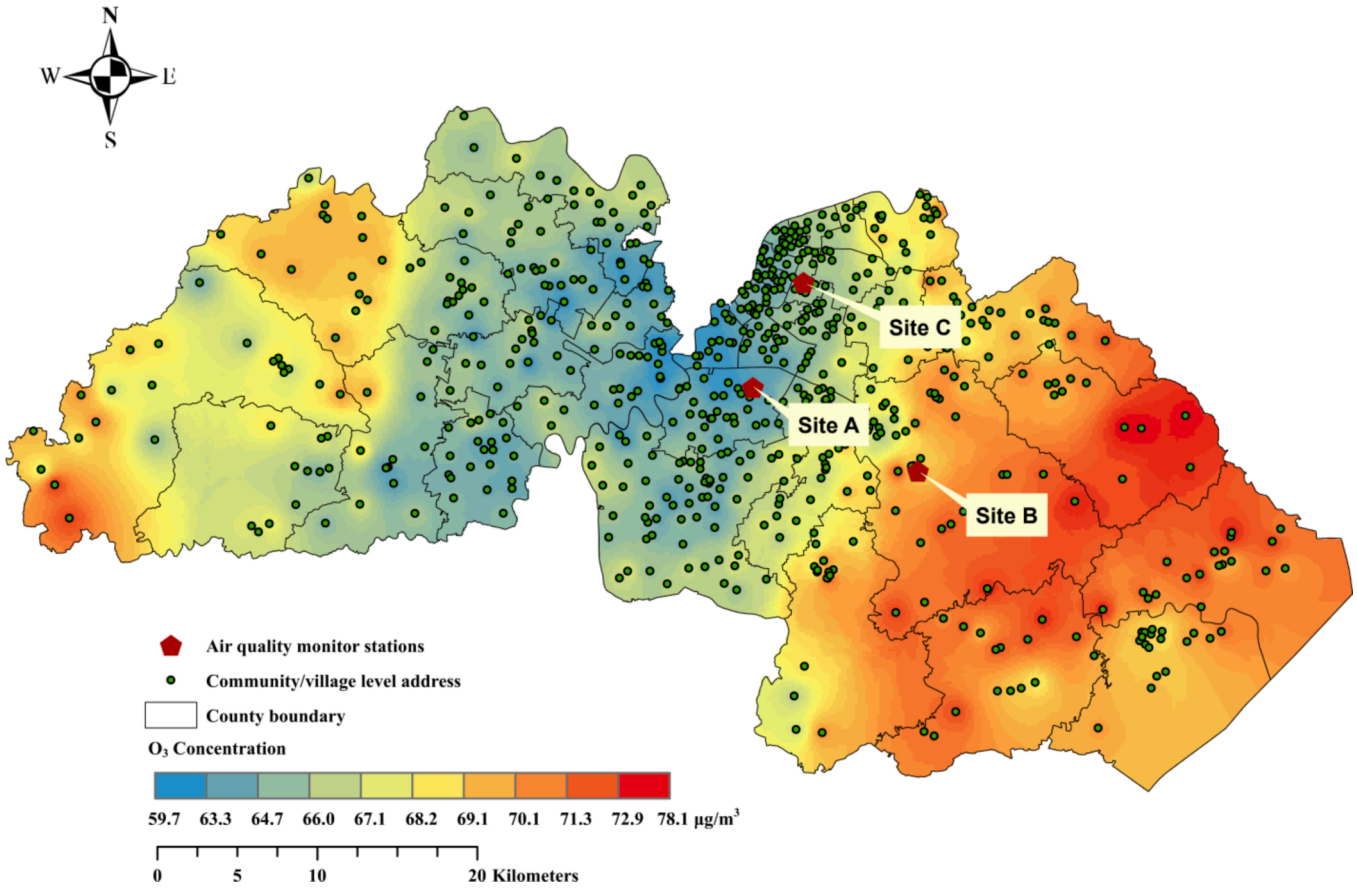

Fig. 1. Spatial Distribution of the Annual Averaged O_3 Concentration in Yinzhou District From 2009 to 2017. Abbreviations: O_3, Ozone.

m^3 increment of annual average O_3 concentrations were examined. Fully adjusted models included the following individual-level variables: age (grouped into 5-year categories), sex, level of education (primary school or lower, middle school, and college or higher), smoking status (never smoker, former smoker, and current smoker), alcohol consumption (never, infrequent, and ≥ 3 times per week), body mass index (BMI: <18.5, 18.5–24.0, and ≥ 24.0 kg/m^2), hypertension status (yes and no), diabetes status (yes and no), urbanicity (urban and rural), as well as the following two county-level variables: healthcare accessibility score (continuous variable) and GDP per capita (continues variable). The proportional hazard assumption was checked using the Schoenfeld residuals (Grambsch PM, 1994). Warm season O_3 exposure (February to October) was also assessed using time-varying Cox model. In addition, we evaluated the concentration–response relationship between O_3 and cause-specific CVD mortality by fitting natural spline in the $PM_{2.5}$-adjusted model. Considering that the concentrations of O_3 was primarily ranged only from 60 to 80 μg/m^3, two degrees of freedom were adopted in the natural spline to avoid overfitting. Subgroup analyses were conducted to examine potential effect modifications by age, sex, smoking status, alcohol consumption, hypertension status, diabetes status, BMI, and urbanicity, separately. Finally, we performed a series of sensitivity analysis by 1) excluding participants who died during the first year after baseline date; 2) using age as a strata variable; 3) excluding hypertension and diabetes status at baseline from model covariates; 4) including temperature as additional model covariate; 5) including normalized difference vegetation index as additional model covariate; 6) using the healthcare accessibility with reassigned scores (3, 2, 1) as model covariate; 7) using different lag patterns for the O_3 exposure: annual average O_3 concentration one year before, the moving two-year average of the O_3 concentration on previous one and two years, and the moving three-year average of the O_3 concentration on previous one, two and three years, respectively; 8) using traditional Cox model with baseline year O_3 concentration; 9) using competing risk model in elders (greater than50 years) who has higher risk of death from CVD and other causes; 10) changing the degree of freedoms for evaluating the concentration–response curve.

All tests were two-sided and P-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA) and R version 3.6.2 (https://www.r-project.org).

3. Results

A total of 744,882 subjects aged over 18 years and who lived in 610 different communities or villages in 33 counties were included in our study (Supplementary Figure 1). The study participants were on average 43.25 years of age, and 50.8% were women. The summary baseline characteristics of the study population are provided in Table 1.

The annual average O_3 concentrations in Yinzhou District during the study period ranged from 59.65 to 78.14 μg/m^3, with a mean exposure of 68.05 ± 2.37 μg/m^3. The average concentrations of warm-season O_3 (February - October) was higher, ranged from 66.14 to 84.28 μg/m^3, with a mean exposure of 73.24 ± 2.37 μg/m^3. For comparison, the corresponding range for annual average $PM_{2.5}$ concentrations was 33.10 – 57.88 μg/m^3 (48.79 ± 3.58 μg/m^3). During the study period, the concentrations of O_3 was generally stable and was relatively high in rural areas, while $PM_{2.5}$ showed a downward trend (Fig. 1, Supplementary Figure 2 and 3).

The correlation coefficient (which ranged from |0.006| to |0.188|) showed a weak correlation between the concentrations of O_3 and $PM_{2.5}$ (Supplementary Figure 3). During the follow-up period (median, 7.72 years), 7,308 subjects died of CVD, of which 1,742 deaths were due to IHD (626 were due to MI), and 4,696 were due to stroke (1,671 were due to hemorrhagic stroke and 1,470 were due to ischemic stroke).

Each 10 μg/m^3 increase in long-term annual average O_3 exposure was associated with an increased risk of CVD mortality (HR: 1.22, 95% CI: 1.12–1.33) in the single pollutant model. The HRs decreased when we used warm season averages O_3 exposure (HR: 1.11, 95% CI: 1.02–1.21). The HR remained almost the same when further adjusting for $PM_{2.5}$ (Table 2). The HRs for death from CVD in different subgroups are shown in Fig. 2. The sensitivity analysis for CVD in elders (greater than 50 years) were conducted using the competing risk model. The result showed that no substantial change occurred when competing events were considered (HR: 1.19, 95% CI: 1.10–1.30), compared with the estimates (HR: 1.18, 95% CI: 1.08–1.29) in the primary analysis. The risk of CVD mortality associated with O_3 exposure was higher among subjects without hypertension (HR: 1.66 vs. 1.15, p = 0.01). We did not observe effect modification by age, sex, smoking status, alcohol consumption, diabetes status, BMI or urbanicity.

Between 60 and 80 μg/m^3, the shape of the associations between the annual average O_3 concentrations and mortality from CVD, IHD, MI, total stroke, hemorrhagic stroke and ischemic stroke were similar (Fig. 3). The association within this range was broadly linear. The sensitivity analysis on different degrees of freedom demonstrated that the pattern of the concentration–response curves was consistent (Supplementary Figure 6).

Table 1
Baseline Characteristics of the Study Population [a].

	Overall (N = 744,882)	Male (N = 366,715)	Female (N = 378,167)
Individual level			
Age (years)	43.25 ± 14.60	43.53 ± 14.40	42.99 ± 14.79
BMI (kg/m^2)			
<18.5	22.218 (2.98)	7982 (2.18)	14,236 (3.76)
18.5–24	556,986 (74.78)	271,966 (74.16)	285,020 (75.37)
≥24	165,678 (22.24)	86,767 (23.66)	78,911 (20.87)
Level of education			
Primary school or lower	218,353 (29.31)	95,130 (25.94)	123,223 (32.58)
Middle school	472,039 (63.37)	245,630 (66.98)	226,409 (59.87)
College or higher	54,490 (7.32)	25,955 (7.08)	28,535 (7.55)
Smoking status			
Never smokers	580,550 (77.94)	222,661 (60.72)	357,889 (94.64)
Former smokers	18,249 (2.45)	15,994 (4.36)	2,255 (0.60)
Current smokers	146,083 (19.61)	128,060 (34.92)	18,023 (4.77)
Alcohol consumption			
Never	636,396 (85.44)	264,072 (72.01)	372,324 (98.45)
Less frequent	38,130 (5.12)	35,311 (9.63)	2819 (0.75)
Frequent (≥3 times/week)	70,356 (9.45)	67,332 (18.36)	3024 (0.80)
Hypertension status	254,899 (34.22)	125,635 (34.26)	129,264 (34.18)
Diabetes status	101,736 (13.66)	48,645 (13.27)	53,091 (14.04)
Urban	519,290 (69.71)	253,382 (69.10)	265,908 (70.31)
County level			
GDP per capita (10,000 US $)	1.99 ± 0.93	2.00 ± 0.93	1.98 ± 0.93
Healthcare accessibility score	4 (2–7)	2 (2–5)	4 (2–12)

Abbreviations: BMI, body mass index; GDP, gross domestic product; US$, U.S. dollar; SD, standard deviation; IQR, inter quartile range.
[a] Data are mean ± SD, n (%) or median (IQR).

Table 2
Hazard Ratio of Cardiovascular Mortality Associated with Ambient O_3 Concentration (per 10 μg/m^3).

Cause of Death	Events	Single pollutant model [a]		$PM_{2.5}$-adjusted model [b]	
		Annual O_3	Warm Season O_3 [c]	Annual O_3	Warm Season O_3 [c]
		1.22 (1.12–1.33)	1.11 (1.02–1.21)	1.22 (1.13–1.33)	1.12 (1.03–1.23)
IHD	1742	1.08 (0.91–1.29)	0.94 (0.78–1.12)	1.08 (0.91–1.29)	0.94 (0.78–1.13)
MI	626	1.24 (0.92–1.66)	1.08 (0.80–1.45)	1.21 (0.90–1.63)	1.11 (0.82–1.50)
Stroke	4696	1.29 (1.16–1.44)	1.17 (1.05–1.31)	1.28 (1.15–1.43)	1.19 (1.06–1.33)
Hemorrhagic stroke	1671	1.41 (1.17–1.69)	1.46 (1.24–1.76)	1.39 (1.16–1.67)	1.49 (1.23–1.80)
Ischemic stroke	1470	1.22 (1.00–1.49)	1.12 (0.91–1.38)	1.22 (1.00–1.49)	1.11 (0.90–1.36)

Abbreviations: CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; O_3, ozone; $PM_{2.5}$, fine particulate matter; BMI, body mass index; GDP, gross domestic product.

[a] Single pollutant model adjusted for age grouping, sex, level of education, smoking status, alcohol consumption, hypertension status, diabetes status, BMI, urbanicity and, county level healthcare accessibility scores and county-level GDP per capita.

[b] $PM_{2.5}$-adjusted model further adjusted $PM_{2.5}$ concentration based on single pollutant model.

[c] Warm season O_3 was defined as the average O_3 concentration from February to October in this study area.

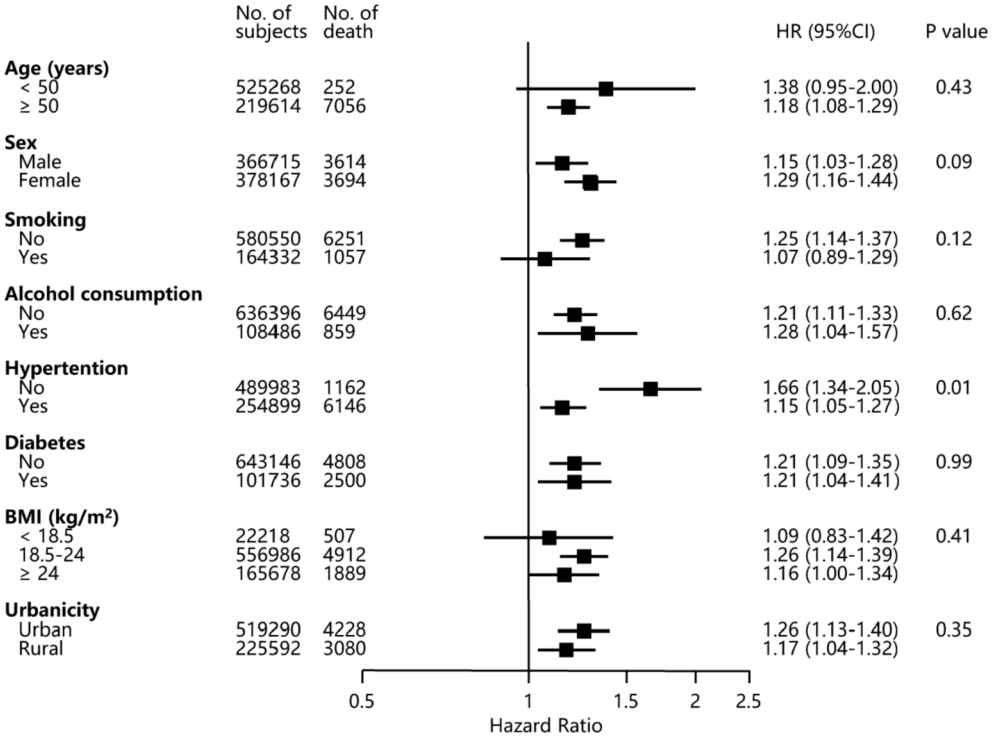

Fig. 2. Hazard Ratio of CVD Mortality Associated with Ambient O_3 Concentration (per 10 μg/m^3), by Category of Selected Risk Factors. Association was adjusted for $PM_{2.5}$ concentration, age grouping, sex, level of education, smoking status, alcohol consumption, hypertension status, diabetes status, BMI, urbanicity and, county-level healthcare accessibility scores and county-level GDP per capita.Abbreviations: O_3, Ozone; $PM_{2.5}$, fine particulate matter;CVD, cardiovascular disease; HR, hazard ratio; BMI, body mass index; GDP, gross domestic product.

With regards to cause-specific CVD mortality, long-term annual average O_3 exposure was not significantly associated with IHD (HR: 1.08, 95% CI: 0.91–1.29) and MI (HR: 1.24, 95% CI: 0.92–1.66) in the single pollutant models. Results using warm season averages O_3 exposure were broadly similar. In single pollutant models, increased O_3-related risks were observed for overall stroke (HR: 1.29, 95% CI: 1.16–1.44), hemorrhagic stroke (HR: 1.41, 95% CI: 1.17–1.69) and ischemic stroke (HR: 1.22, 95% CI: 1.00–1.49). Warm season O_3 as exposure reduced the HR estimates for ischemic stroke (HR: 1.12, 95% CI: 0.91–1.38). We also noted similar associations for all these outcomes in $PM_{2.5}$-adjusted models (Table 2).

A series of sensitivity analyses were conducted. All these estimates were broadly similar to those of our main model (Supplementary Table 2), suggesting that our results were robust.

4. Discussion

This study showed that long-term exposure to high O_3 concentrations is associated with increased risk of mortality from CVD and stroke (including both hemorrhagic and ischemic stroke) in a Chinese population, independent of $PM_{2.5}$ and other traditional CVD risk factors. Using high resolution exposure of O_3 concentrations linking to a large Chinese cohort with detailed individual-level information, our study provided epidemiological evidence for positive associations between long-term O_3 exposure and cause-specific CVD mortality.

As briefly mentioned in the introduction, in terms of the association between long-term O_3 exposure and healthy outcomes, several studies have reported that there may be a concentration–response curve threshold, above which a higher risk is observed (Lim et al., 2019; Turner et al., 2016; Weichenthal et al., 2017). The recent Canadian Census Health and Environment Cohort (CanCHEC) study (Weichenthal et al., 2017) observed the threshold at 25 μg/m^3. Above this threshold, the estimates of CVD mortality increased with O_3 concentration. The American Cancer Society Cancer Prevention Study II (CPS-II) (Turner et al., 2016) and the National Institutes of Health-American Association of Retired Persons Diet and Health Study (Lim et al., 2019) in America also reported similar non-linear relationship with thresholds of 35 μg/m^3 and 40 μg/m^3, respectively. A study by Jerrett et al (Jerrett et al., 2009) observed an O_3 concentration threshold at 60 μg/m^3 for respiratory mortality in the CPS-II cohort. Therefore, one of the possible

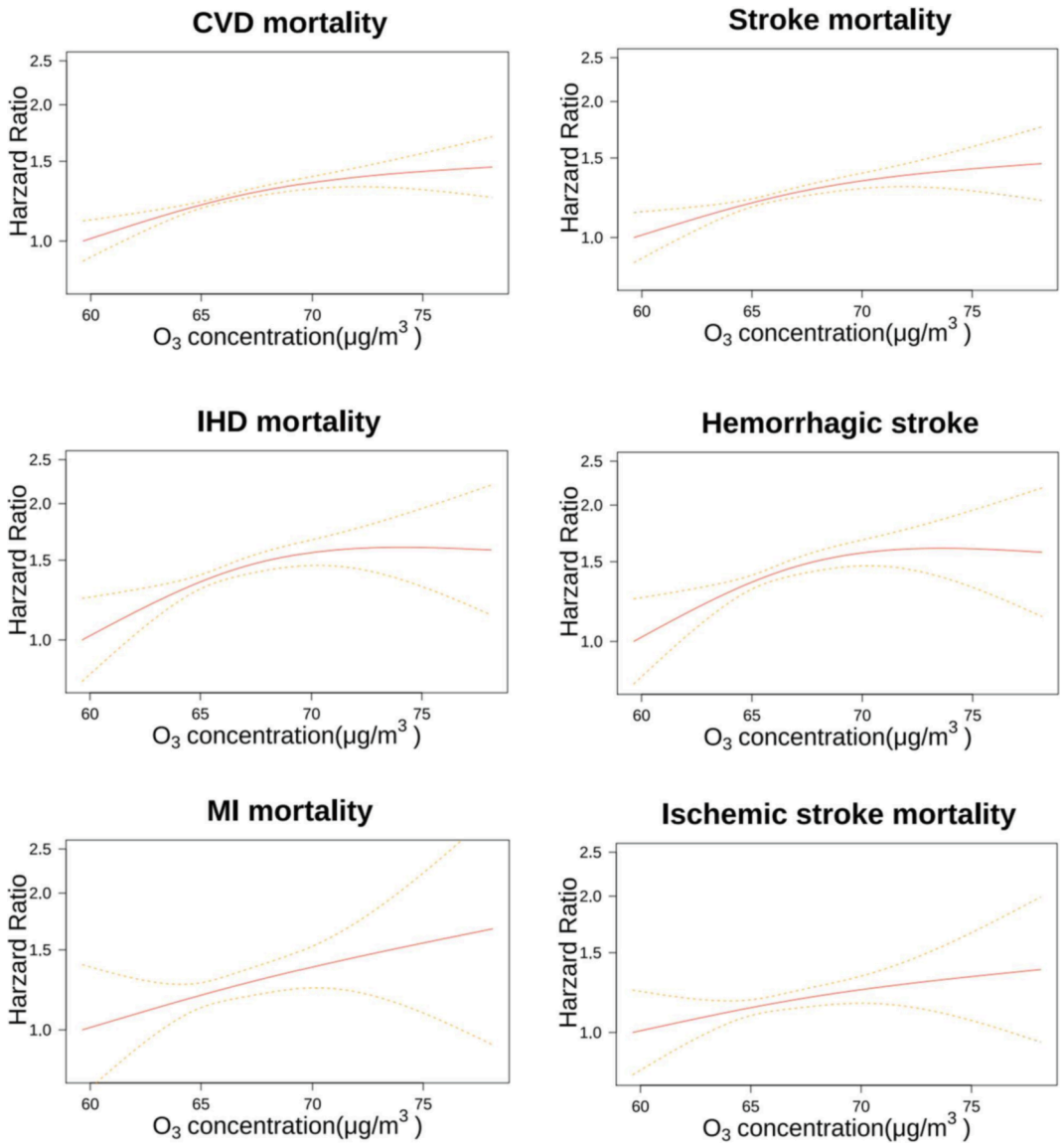

Fig. 3. Association between Annual Average O_3 Concentration and Cause-specific CVD Mortality. Abbreviations: CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; O_3, Ozone; $PM_{2.5}$, fine particulate matter.

important reasons that previous studies have inconclusive results is because O_3 concentrations in these studies in the developed countries were generally below 60 μg/m^3. Moreover, if the proposed non-linear relationship exists, the overall estimation for the low range of O_3 exposure assuming linearity might underestimate the effect when the exposure level increases. For example, studies from U.S. and Canada reported significant and positive associations between long-term O_3 exposure below 60 μg/m^3 and CVD outcomes, with an HR of 1.03 (95% CI: 1.01–1.05) for CVD mortality from the CPS-II study (Turner et al., 2016) and an HR of 1.03 (95% CI: 1.02–1.04) from the CanCHEC study (Cakmak et al., 2016). Although the estimates of O_3-related CVD mortality reported by these studies were lower, it is likely that the association could be stronger at higher level of O_3 concentrations according to the shape of concentration–response curve in these studies.

In this study, we used a spatial temporal resolution up to 1 × 1 km for the O_3 estimates as the primary exposure. It has been reported that high resolution of air pollution estimates could reveal greater association with the outcome (Crouse et al., 2020). We also estimated the associations between long-term $PM_{2.5}$ exposure and cause-specific CVD mortality in the same analysis set in our study. The estimates (Supplementary Table 3) were similar to the recent study examining long-term $PM_{2.5}$ exposure across China (Liang et al., 2020a). This demonstrated the credibility of our main findings on long-term O_3 exposure. Meanwhile, it has been noted that the association might also be affected by the correlation between O_3 and $PM_{2.5}$ (Kazemiparkouhi et al., 2020). $PM_{2.5}$ concentrations could also differentially confound O_3-mortality associations (Jerrett et al., 2009). We only observed a weak correlation between O_3 and $PM_{2.5}$, and our results show that the association of O_3 remained robust after the adjustment of $PM_{2.5}$ in our study.

Most relevant studies from the US and Canada used warm-season O_3 as the primary exposure (Cakmak et al., 2018; Di et al., 2017; Kazemiparkouhi et al., 2020). Generally speaking, the O_3 concentration is higher in the warm season, which may lead to stronger health effects. This is often the case when the study area has clear seasonal changes and covers a vast area with large regional disparities in O_3 concentration. However, in our study, the estimates when we use warm-season average O_3 concentration (February to October) were lower than those using the annual average O_3 concentration. As can be seen from the monthly O_3 concentration (supplementary Figure 5), the O_3 concentration in summer in our study area was not highest due to large number of rainy days. The subtropical monsoon from the western Pacific Ocean decreases the O_3 concentration and further eliminates the regional disparity.

Several biological mechanisms have been proposed to explain the relationship between O_3 exposure and CVD mortality. Oxidative stress caused by O_3 is suggested as the first hierarchical response in humans (Rajagopalan et al., 2018), followed by activation of systematic inflammation (Münzel et al., 2017; Sun et al., 2008). Inflammatory mediators can enter the circulatory system, stimulate the release of coagulation factors (Goodman et al., 2015), impair vascular function (Breton et al., 2012) and increase thrombosis (Rajagopalan et al., 2018), which may promote IHD and, leading to CVD mortality. Moreover, O_3 exposure may cause adverse health effects in a dose-dependent manner and exposure to high concentrations of O_3 may lead to high estimates of health effects. An experimental study (Lakey et al., 2016) found that an increase of O_3 from<30 ppb to more than 100 ppb can reduce the chemical half-life of antioxidants surfactants in human epithelial lining fluid, suggesting that high O_3 concentrations exposure can cause severe oxidative stress, not only as a result of high levels of reactive oxygen species but also as a result of low levels of antioxidant and surfactant concentrations. An epidemiology study of atherosclerosis-related biomarkers (Poursafa et al., 2011) reported an increased in tissue factor levels and a decreased in thrombomodulin levels with increased O_3 exposure. To identify the potential biological pathways connecting long-term O_3 exposure to CVD mortality, future investigations are still needed to fill the critical gaps in the health evidence.

The study has several important strengths that should be noted. First, the high spatiotemporal resolution of the exposure assessment helped us capture fine-scale variations in O_3 (and $PM_{2.5}$) concentrations. Second, we included a large sample of subjects (more than 700,000) from China in the epidemiological studies of air pollution, enabling high power for the estimation of not only the overall CVD mortality risks, but also cause-specific CVD mortality outcomes, such as IHD, MI, overall stroke, hemorrhagic stroke and ischemic stroke. In addition, our study included detailed individual-level variables, which were vital to reduce confounding, but that are often unavailable in most studies with large simple size.

This study also has several limitations that should be acknowledged. First, the O_3 concentration range (from 60 to 80 μg/m^3) as well as the $PM_{2.5}$ concentration range (from 30 to 60 μg/m^3) due to the regional coverage in our study area may limit the generalizability of our findings to the other range of exposure. Second, despite our efforts to use the high-resolution estimates of O_3 (and $PM_{2.5}$) concentrations, there may exist some misspecification of exposure due to the community/village-level addresses of participants. However, such exposure error has been shown to attenuate effect estimates (Crouse et al., 2020; Hvidtfeldt et al., 2019), indicating that our main estimates may still be conservative. Third, other ambient air pollutants, such as nitrogen dioxide, sulfur dioxide, and carbon monoxide, were not included in our analysis because no high-resolution exposure estimates were available at this granularity. It is still possible that they may confound the association between O_3 exposure and mortality in different ways. Fourth, potential selection bias in the population may exist because 308,683 subjects (29% of the original cohort) were excluded, most of whom were younger and less frequently had hypertension and diabetes mellitus (Supplementary Table 1).

5. Conclusion

The results of the study provide new epidemiological evidence to support the positive and independent association between long-term O_3 exposure and cause-specific CVD mortality when concentration of O_3 is high. Our results suggest that there is an urgent need to control ambient O_3 pollution for CVD protection, especially in developing countries.

Ethical approval

This study was approved by the Peking University Institutional Review Board (IRB00001052-16011).

CRediT authorship contribution statement

Shudan Liu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yi Zhang:** Data curation, Resources, Writing – review & editing. **Runmei Ma:** Data curation, Resources. **Xiaofei Liu:** Data curation, Investigation, Writing – review & editing. **Jingyuan Liang:** Data curation, Investigation, Writing – review & editing. **Hongbo Lin:** Project administration, Resources. **Peng Shen:** Project administration, Resources. **Jingyi Zhang:** Software. **Ping Lu:** Software. **Xun Tang:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. **Tiantian Li:** Resources, Supervision, Validation, Writing – review & editing. **Pei Gao:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, 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.

Acknowledgements

This study was supported by the Ministry of Science and Technology of the People's Republic of China (grant number 2020YFC2003503) and the National Natural Science Foundation of China (grant number 81973132).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107280.

References

Bentayeb, M., Wagner, V., Stempfelet, M., Zins, M., Goldberg, M., Pascal, M., Larrieu, S., Beaudeau, P., Cassadou, S., Eilstein, D., Filleul, L., Le Tertre, A., Medina, S., Pascal, L., Prouvost, H., Quénel, P., Zeghnoun, A., Lefranc, A., 2015. Association between long-term exposure to air pollution and mortality in France: A 25-year follow-up study. Environ. Int. 85, 5–14.

Berman, J.D., Fann, N., Hollingsworth, J.W., Pinkerton, K.E., Rom, W.N., Szema, A.M., Breysse, P.N., White, R.H., Curriero, F.C., 2012. Health benefits from large-scale ozone reduction in the United States. Environ. Health Perspect. 120 (10), 1404–1410.

Breton, C.V., Wang, X., Mack, W.J., Berhane, K., Lopez, M., Islam, T.S., Feng, M., Lurmann, F., McConnell, R., Hodis, H.N., Künzli, N., Avol, E.d., 2012. Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation 126 (13), 1614–1620.

Cakmak, S., Hebbern, C., Pinault, L., Lavigne, E., Vanos, J., Crouse, D.L., Tjepkema, M., 2018. Associations between long-term PM2.5 and ozone exposure and mortality in the Canadian Census Health and Environment Cohort (CANCHEC), by spatial synoptic classification zone. Environ. Int. 111, 200–211.

Cakmak, S., Hebbern, C., Vanos, J., Crouse, D.L., Burnett, R., 2016. Ozone exposure and cardiovascular-related mortality in the Canadian Census Health and Environment Cohort (CANCHEC) by spatial synoptic classification zone. Environ. Pollut. 214, 589–599.

Carey, I.M., Atkinson, R.W., Kent, A.J., Van Staa, T., Cook, D.G., Anderson, H.R., 2013. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am. J. Respir. Crit. Care Med. 187, 1226–1233. https://doi.org/10.1164/rccm.201210-1758OC.

GBD 2017 Causes of Death Collaborators, 2018. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1736–1788. https://doi.org/10.1016/s0140-6736(18)32203-7.

GBD 2019 Risk Factors Collaborators, 2019. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 396, 1223–1249. https://doi.org/10.1016/s0140-6736(20)30752-2.

Crouse, D.L., Erickson, A.C., Christidis, T., Pinault, L., van Donkelaar, A., Li, C., Meng, J., Martin, R.V., Tjepkema, M., Hystad, P., Burnett, R., Pappin, A., Brauer, M., Weichenthal, S., 2020. Evaluating the Sensitivity of PM2.5-Mortality Associations to the Spatial and Temporal Scale of Exposure Assessment. Epidemiology 31 (2), 168–176.

Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., Dominici, F., Schwartz, J.D., 2017. Air Pollution and Mortality in the Medicare Population. The New England J. Med. 376 (26), 2513–2522.
Ensor, K.B., Raun, L.H., Persse, D., 2013. A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. Circulation 127, 1192–1199. https://doi.org/10.1161/circulationaha.113.000027.
Goodman, J.E., Prueitt, R.L., Sax, S.N., Pizzurro, D.M., Lynch, H.N., Zu, K.e., Venditti, F. J., 2015. Ozone exposure and systemic biomarkers: Evaluation of evidence for adverse cardiovascular health impacts. Crit. Rev. Toxicol. 45 (5), 412–452.
Grambsch PM, T.T., 1994. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81, 515–526. https://doi.org/10.1093/biomet/82.3.668.
Heal, M.R., Heaviside, C., Doherty, R.M., Vieno, M., Stevenson, D.S., Vardoulakis, S., 2013. Health burdens of surface ozone in the UK for a range of future scenarios. Environ. Int. 61, 36–44. https://doi.org/10.1016/j.envint.2013.09.010.
Hvidtfeldt, U.A., Sørensen, M., Geels, C., Ketzel, M., Khan, J., Tjønneland, A., Overvad, K., Brandt, J., Raaschou-Nielsen, O., 2019. Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. Environ. Int. 123, 265–272.
Jerrett, M., Burnett, R.T., Pope, C.A., Ito, K., Thurston, G., Krewski, D., Shi, Y., Calle, E., Thun, M., 2009. Long-term ozone exposure and mortality. The New England J. Med. 360 (11), 1085–1095.
Jhun, I., Fann, N., Zanobetti, A., Hubbell, B., 2014. Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ. Int. 73, 128–134. https://doi.org/10.1016/j.envint.2014.07.009.
Kazemiparkouhi, F., Eum, K.D., Wang, B., Manjourides, J., Suh, H.H., 2020. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. J. Expo. Sci. Environ. Epidemiol. 30, 650–658. https://doi.org/10.1038/s41370-019-0135-4.
Lakey, P.S., Berkemeier, T., Tong, H., Arangio, A.M., Lucas, K., Pöschl, U., et al., 2016. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. Sci. Rep. 6, 32916. https://doi.org/10.1038/srep32916.
Liang, F., Liu, F., Huang, K., Yang, X., Li, J., Xiao, Q., et al., 2020a. Long-Term Exposure to Fine Particulate Matter and Cardiovascular Disease inChina. J. Am. Coll. Cardiol. 75, 707–717. https://doi.org/10.1016/j.jacc.2019.12.031.
Likhvar, V.N., Pascal, M., Markakis, K., Colette, A., Hauglustaine, D., Valari, M., Klimont, Z., Medina, S., Kinney, P., 2015. A multi-scale health impact assessment of air pollution over the 21st century. Sci. Total Environ. 514, 439–449.
Lim, C.C., Hayes, R.B., Ahn, J., Shao, Y., Silverman, D.T., Jones, R.R., Garcia, C., Bell, M. L., Thurston, G.D., 2019. Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. Am. J. Respir. Crit. Care Med. 200 (8), 1022–1031.
Lin, H., Tang, X., Shen, P., Zhang, D., Wu, J., Zhang, J., Lu, P., Si, Y., Gao, P., 2018. Using big data to improve cardiovascular care and outcomes in China: a protocol for the CHinese Electronic health Records Research in Yinzhou (CHERRY) Study. BMJ Open 8 (2), e019698. https://doi.org/10.1136/bmjopen-2017-019698.
Ma, R., Ban, J., Wang, Q., Zhang, Y., Yang, Y., He, M.Z., Li, S., Shi, W., Li, T., 2021a. Random forest model based fine scale spatiotemporal O(3) trends in the Beijing-Tianjin-Hebei region in China, 2010 to 2017. Environ. Pollut. 276, 116635. https://doi.org/10.1016/j.envpol.2021.116635.
Ma, R., Ban, J., Wang, Q., Zhang, Y., Yang, Y., Li, S., et al., 2021b. Full-coverage 1 km daily ambient PM2.5 and O3 concentrations of China in 2005–2017 based on multi-variable random forest model. Earth Syst. Sci. Data Discuss. 2021, 1–28. https://doi.org/10.5194/essd-2021-296.
Münzel, T., Sørensen, M., Gori, T., Schmidt, F.P., Rao, X., Brook, F.R., et al., 2017. Environmental stressors and cardio-metabolic disease: part II-mechanistic insights. Eur. Heart J. 38, 557–564. https://doi.org/10.1093/eurheartj/ehw294.
Poursafa, P., Kelishadi, R., Lahijanzadeh, A., Modaresi, M., Javanmard, S.H., Assari, R., Amin, M.M., Moattar, F., Amini, A., Sadeghian, B., 2011. The relationship of air pollution and surrogate markers of endothelial dysfunction in a population-based sample of children. BMC Public Health 11 (1). https://doi.org/10.1186/1471-2458-11-115.
Pu, X., Wang, T.J., Huang, X., Melas, D., Zanis, P., Papanastasiou, D.K., Poupkou, A., 2017. Enhanced surface ozone during the heat wave of 2013 in Yangtze River Delta region, China. Sci. Total Environ. 603-604, 807–816.
Rajagopalan, S., Al-Kindi, S.G., Brook, R.D., 2018. Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 72, 2054–2070. https://doi.org/10.1016/j.jacc.2018.07.099.
Sun, Q., Yue, P., Ying, Z., Cardounel, A.J., Brook, R.D., Devlin, R., Hwang, J.-S., Zweier, J.L., Chen, L.C., Rajagopalan, S., 2008. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. Arterioscler. Thromb. Vasc. Biol. 28 (10), 1760–1766.
Turner, M.C., Jerrett, M., Pope, C.A., Krewski, D., Gapstur, S.M., Diver, W.R., Beckerman, B.S., Marshall, J.D., Su, J., Crouse, D.L., Burnett, R.T., 2016. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. Am. J. Respir. Crit. Care Med. 193 (10), 1134–1142.
Zhou, Y, Duan, W, Chen, Y, Yi, J, Wang, B, Di, Y, He, C, 2022. Exposure Risk of Global Surface O_3 During the Boreal Spring Season. Exposure and Health 29, 1–16. https://doi.org/10.1007/s12403-022-00463-7.
U.S. EPA, 2020. Integrated science assessment (ISA) for ozone and related photochemical oxidants (final report). Washington, DC: U.S. Environmental Protection Agency, 2020. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=348522.
Wang, J.-B., Gu, M.-J., Shen, P., Huang, Q.-C., Bao, C.-Z., Ye, Z.-H., Wang, Y.-Q., Mayila, M., Ye, D., Gu, S.-T., Lin, H.-B., Chen, K., 2016. Body Mass Index and Mortality: A 10-Year Prospective Study in China. Sci. Rep. 6 (1) https://doi.org/10.1038/srep31609.
Weichenthal, S., Pinault, L.L., Burnett, R.T., 2017. Impact of Oxidant Gases on the Relationship between Outdoor Fine Particulate Air Pollution and Nonaccidental, Cardiovascular, and Respiratory Mortality. Sci. Rep. 7, 16401. https://doi.org/10.1038/s41598-017-16770-y.
Xu, Y., Ramanathan, V., Victor, D.G., 2018. Global warming will happen faster than we think. Nature 564, 30–32. https://doi.org/10.1038/d41586-018-07586-5.
Zhao, C., Wang, Q., Ban, J., Liu, Z., Zhang, Y., Ma, R., Li, S., Li, T., 2020. Estimating the daily PM(2.5) concentration in the Beijing-Tianjin-Hebei region using a random forest model with a $0.01^\circ \times 0.01^\circ$ spatial resolution. Environ. Int. 134, 105297. https://doi.org/10.1016/j.envint.2019.105297.