Association of long-term exposure to ozone with cardiovascular mortality and its metabolic mediators: evidence from a nationwide, population-based, prospective cohort study

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Summary

Background Previous studies about chronic effects of ozone (O_3) on cardiovascular mortality are scarce and inconclusive. We aimed to investigate the association between cardiovascular mortality and a broad range of long-term O_3 exposure levels.

Methods This analysis included 3,206,871 participants aged 35–75 years enrolled in the ChinaHEART study. Participants were recruited from the 31 provinces of the Chinese mainland between January 2015 and December 2020. The five-year average O_3 concentrations before baseline visits were calculated to represent long-term exposure.

Findings Over a median follow-up period of 4.7 (interquartile range: 3.7–6.2) years, 35,553 (1.1%) participants died from cardiovascular diseases (CVD). Following multivariable adjustment, nonlinear relationships were identified between O_3 concentrations and CVD and ischemic heart disease (IHD) mortality, with inflection points at 85.44 and 88.15 μg/m^3, respectively. Above these points, a 10.0 μg/m^3 increase in the O_3 level was associated with a 13.9% (hazard ratio [HR]: 1.139, 95% confidence interval [CI]: 1.096–1.184) and 25.0% (HR: 1.250, 95% CI: 1.151–1.357) greater risk of CVD and IHD mortality, respectively. Conversely, O_3 exposure exhibited a linear relationship with ischemic stroke mortality. Moreover, the metabolic factors explained more than half of the association between O_3 exposure and CVD mortality.

Interpretation Substantial influences of long-term O_3 exposure on CVD mortality were identified, with notable mediation proportions attributed to metabolic factors. These findings could facilitate the air quality standard revisions and risk reduction strategy making in the future.

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Research in context

Evidence before this study

We searched PubMed for literature on long-term ozone exposure and cardiovascular mortality published in English before March 19, 2024, using the medical subject heading terms "mortality" OR "death", and combined search terms "ozone" OR "O_3" OR "air pollution" OR "air pollutant*", and "cardiovascular disease" OR "coronary artery disease" OR "coronary disease" OR "coronary heart disease" "stroke", and "long-term". We reviewed the references cited in the related papers as an addition. We found several studies have reported the chronic effects of O_3 exposure on cardiovascular mortality. However, the previous studies primarily originated from developed counties and seldom incorporated individual-level measurements, and the findings were inconsistent. However, the existing evidence only estimated the overall effect assuming linearity even the nonlinear exposure-response relationship exists, which might significantly underestimate the health effects of O_3 on CVD mortality. Besides this, knowledge remains scare regarding whether and to what extent metabolic factors (i.e., hypertension, diabetes, dyslipidemia, and obesity) mediate the relationship between ozone and cardiovascular mortality.

Added value of this study

This study has substantially deepened understanding for the chronic effects of O_3 exposure on cardiovascular mortality. In this study of 3.2 million Chinese community-based participants aged 35–75 years, the nonlinear relationships were found between O_3 concentrations and mortality due to cardiovascular disease and ischemic heart disease, with a 15.4% and 21.5% greater risk per 10.0 μg/m^3 above the inflection points at 85.20 and 88.39 μg/m^3, respectively. However, no significant association were observed below the inflection points. In contrast, long-term O_3 exposure linearly related to stroke mortality. The association between O_3 exposure and cardiovascular mortality were more prominent in the elderly (aged 65 years and above), those lived in rural areas, and farmers. Notably, the metabolic factors accounted for over half of the association between O_3 exposure and cardiovascular mortality.

Implications of all the available evidence

Our study identified substantial effects of long-term O_3 exposure on CVD mortality, with notable mediation effects attributed to metabolic factors, which helps better understand the health effects of O_3 on cardiovascular system and provides fresh evidence for more accurate estimations of disease burden. Furthermore, comprehensively assessing the association between long-term O_3 exposure and cardiovascular mortality is crucial for establishing annual air quality guidelines (AQG), despite short-term (8-h) daily maximum and peak season AQG level for O_3 have been established. It is also noteworthy that there is an urgent need for governments to implement targeted policies and interventions aimed at lowering the prevalence of diabetes, hypertension, dyslipidemias, general obesity, and abdominal obesity to alleviate the potential influence of O_3 on cardiovascular mortality.

Introduction

Ozone (O_3), as a major ambient pollutant, has caused a heavy disease burden.[1] In 2019, more than 0.36 million premature deaths globally were attributed to long-term O_3 exposure, solely based on its association with mortality from chronic obstructive pulmonary disease observed in developed counties.[2] However, this is evidently underestimated considering that: 1) O_3 may be associated with other specific causes of death like cardiovascular diseases (CVD)[3–5]; 2) O_3 pollution is even severe in low-income and middle-income countries.[2] Furthermore, despite significant reductions in the exposure levels of most air pollutants due to collaborative efforts in many countries,[6] the annual average concentration of O_3 is gradually rising worldwide due to global warming,[1,2] posing an escalating threat to public health.

The causal relationship between long-term O_3 exposure and respiratory mortality has been established, but not for CVD mortality.[7] Despite some studies investigating the link between long-term O_3 exposure and CVD mortality, the evidence remains limited and inconsistent. Studies from the US and Canada have shown an increased risk of CVD mortality with long-term O_3 exposure,[8–10] while several cohort studies from the UK, Denmark, and France found either no association or an inverse one.[11–13] One plausible explanation is that the relationship between long-term O_3 exposure and CVD mortality is nonlinear, with a threshold concentration ranging from 35 to 40 ppb.[10,14] However, the existing evidence primarily originates from developed countries where O_3 levels are typically below 40 ppb.[10–12]

In addition, understanding the evolution and intermediate factors, particularly the modifiable metabolic risk factors, in the association between long-term O_3 exposure and CVD mortality, is crucial for implementing targeted efforts to promote health and reduce the disease burden. Cardiometabolic risk factors such as hypertension, diabetes, dyslipidemia, and obesity have long been hypothesized to mediate the relationship between air pollution and CVD.[15] However, the existing

evidence on this topic is quite limited. Several studies have suggested that long-term O_3 exposure is associated with these metabolic diseases.[16–19] And a recent study found that dyslipidemia partly mediates the association between long-term O_3 exposure and arterial stiffness.[20] Furthermore, a cross-sectional study indicates that the relationship between O_3 exposure and the prevalence of CVD is mediated by elevated systolic and diastolic blood pressure (BP) as well as increased triglycerides (TG) levels.[18] Taking together, these results imply that O_3 may indirectly contribute to CVD mortality. However, previous studies have seldom incorporated individual-level measurements to assess whether these factors mediate the influence of O_3 on CVD mortality.[10–12,21–25] Thus, the existing evidence is considered lacking in persuasiveness.

To fill these knowledge gaps, we utilized data from the China Health Evaluation And risk Reduction through nationwide Teamwork (ChinaHEART) project to examine the relationship between long-term O_3 exposure and CVD mortality, including its subcategories. Furthermore, we assessed whether hypertension, diabetes, dyslipidemia, and obesity mediated the association.

Methods

Study design and participants

The ChinaHEART project, a nationwide population-based public health program funded by the Chinese government, is designed to identify and intervene in the population with high cardiovascular disease risk factors. The project's design has been outlined previously (formerly named China PEACE MPP).[26] Briefly, between 1 January 2015 and 31 December 2020, the project identified 292 study sites (173 rural counties, 119 urban districts) across the 31 provinces of Chinese mainland to ensure diversity in geographic distribution, population structure, and exposure to risk factors and disease patterns (Supplementary Method). Residents aged 35–75 years in the community who had lived in the study site for more than 6 months in the preceding year were invited to participate. To date, over 4 million individuals have been enrolled in the cohort study, with a response rate exceeding 35%, which is higher than similar population studies conducted in China and Europe.[27] The project was approved by the central ethics committee at the China National Center for Cardiovascular Diseases (approval no. 2014-574). All registered participants provided written informed consent.

In this study, 3,852,856 participants were initially assessed. After excluding 378,361 participants with unavailable O_3 data, 634 having incomplete data for the date of death, and 266,990 participants with extreme values for body mass index (BMI) (defined as BMI <15 kg/m^2 or BMI >40 kg/m^2) or waist circumference (WC) (defined as WC <50 cm or WC >150 cm), ultimately, a total of 3,206,871 participants were included in the study (Supplementary Figure S1).

Data collection and variable definition

At the baseline visits, participants' sociodemographic information (i.e., age, sex, education level, marital status, occupation, annual household income and health insurance), lifestyle factors (smoking and alcohol consumption), self-reported medical history (i.e., hypertension, diabetes, and dyslipidemia), and medication use (i.e., antihypertensive drugs, hypoglycaemic agents, and lipid-lowering agents) were collected through an in-person interview conducted by trained personnel. Specifically, tobacco smoking status was classified as never, former and current smoking, and alcohol consumption status was categorized according to the alcohol drinking frequency. We defined an alcohol drinker as participants who had consumed alcohol ≥2 times per month (detailed in the Supplementary Methods).

All the metabolic parameters were measured at baseline using standardized protocols and unified devices. Briefly, participants were instructed to wear lightweight clothing and refrain from wearing shoes or caps during weight and height measurements. The BMI was calculated as weight in kilograms divided by the square of height in meters. WC was measured midway between the lower edge of the costal arch and the upper edge of the iliac crest, rounded to the nearest 0.1 cm. BP was measured twice on their right upper arm after a 5-min of rest in a seated position using a standardized electronic blood pressure monitor. If the difference between the two systolic BP measurements was larger than 10 mmHg, a third measurement was taken, and the average of the last two readings was used. The concentrations of total cholesterol (TC), TG and high-density lipoprotein (HDL) were tested using a rapid lipid analyzer. Low-density lipoprotein (LDL) levels were calculated using the Friedewald equation.[28] Blood glucose levels were tested using a rapid blood glucose analyzer.

General obesity was defined as a BMI of 28.0 kg/m^2 or higher, and abdominal obesity was defined as elevated WC (≥90 cm in men or ≥85 cm in women) according to Chinese criteria.[29] Diabetes was defined as a self-reported disease history of diabetes or receiving hypoglycaemic agents. Hypertension was defined as systolic/diastolic BP ≥140/90 mmHg, self-reported disease history of hypertension, or recent use of antihypertensive drugs.[30] Dyslipidemia was defined as elevated TC (≥6.2 mmol/L), or LDL (≥4.1 mmol/L), or TG (≥1.7 mmol/L), or decreased HDL (<1.0 mmol/L), or a self-reported history of dyslipidemia, or receiving the lipid-lowering agents.[31]

Exposure assessment

Ambient O_3 and fine particulate matter ($PM_{2.5}$) concentration data were obtained from the ChinaHighAirPollutants (CHAP) dataset (available at https://weijing-rs.github.

io/product.html) with high temporal (daily) and spatial resolutions (1 km × 1 km).[32–34] Briefly, both the O_3 and $PM_{2.5}$ concentrations from the CHAP dataset were estimated by integrating the ground-based, satellite remote sensing, atmospheric reanalysis, and model emission datasets into extended ensemble learning of the space-time machine learning models, being highly consistent with the air pollution monitoring stations (sample-based: cross-validated R^2 = 0.92 and 0.89 for daily $PM_{2.5}$ and O_3) (detailed in Supplementary Methods).[32–34] In this study, each participant's annual O_3 and $PM_{2.5}$ exposure were determined by matching their residential address with the corresponding grid cell. The five-year average O_3 and $PM_{2.5}$ concentrations prior to the baseline visits were calculated as the long-term exposure.

Study outcomes

In this study, we obtained vital status and causes of death for participants through a passive follow-up process. This involved linking cohort data with the National Mortality Surveillance System and Vital Registration of Chinese Center for Disease Control and Prevention (CDC) using participants' ID number. This system encompasses both urban and rural areas across all 31 mainland provinces of China and provides high-quality, near-real-time data, with updates available up to December 31, 2022. Death records are reported by healthcare institutions shortly after a death occurs, ensuring the timely capture of information. These reports are then verified annually against local residential records and health insurance records, which enhances the accuracy and completeness of mortality data. Additionally, the system incorporates quality control measures, including periodic audits and data validation processes, to minimize misclassification and ensure consistency in cause-of-death reporting.

The death records in this system were mainly coded according to the 10th edition of the International Classification of Diseases (ICD-10). The outcomes of interest in the current analysis were CVD mortality (ICD-10: I01–I99) and its respective subtypes, including death due to ischemic heart disease (IHD) (ICD-10: I20–I25), ischemic stroke (IS) (ICD-10: I63), and hemorrhagic stroke (HS) (ICD-10: I60–I62).

Statistical analysis

Participants' characteristics according to the quartiles (Q) of O_3 concentrations were presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables and counts (percentages) for categorical variables. To compare the differences among Q1–4 of O_3 concentrations, one-way Analysis of Variance, Kruskal–Wallis tests, and Chi-Square (χ^2) tests were performed as appropriate.

Cox proportional hazards models were employed to assess the association between long-term O_3 exposure and CVD mortality, yielding hazard ratios (HRs) and 95% confidence intervals (CIs). A directed acyclic graph (DAG) was used to select covariates (Supplementary Methods), and we identified smoking, alcohol consumption, and medical insurance as the mediator-outcome confounders.[35] Therefore, adjusted covariates in the Cox models comprised age, sex, urbanity, region, season, income, occupation, education, marital status, temperature, humidity, and elevation, and only the variable for elevation had missing data, with a total of 100 missing values (0.0031%). The proportional hazards assumption of each included variable in the models was checked with the Schoenfeld residual test, and no violations were observed. The linearity assumption of all continuous covariates in the models was evaluated by Martingale residuals plots, revealing an obvious nonlinear relationship for humidity and temperature. Therefore, standard methods such as fractional polynomials and regression splines were employed to handle these continuous variables (Supplementary Methods).[36,37] Additionally, to examine whether the relationships of O_3 with CVD mortality were confounded by $PM_{2.5}$, we constructed a two-pollutant model by adding the five-year average $PM_{2.5}$ concentrations of participants into Cox proportional-hazards regression models. To explore the exposure-response relationship between O_3 levels and CVD mortality, restricted cubic splines (RCS) with three knots, which were determined by Akaike information criterion (AIC) and Bayesian information criterion (BIC) values (Supplementary Table S1), at 10th, 50th, and 90th percentiles incorporated in the fully adjusted Cox regression models were conducted.[38,39] If the relationship was found to be nonlinear, a recursive algorithm was employed to determine the inflection point between O_3 exposure and CVD mortality. Specifically, we identified the inflection point by progressively narrowing the range and refining calculations to find the point that maximizes the model's log-likelihood function (detailed in Supplementary Methods). Subsequently, a two-segment Cox proportional hazards model was applied on both sides of the inflection point to investigate the association between long-term O_3 exposure and CVD mortality. Mediation analyses were conducted using the public %MEDIATE SAS macro (https://ysph.yale.edu/cmips/research/software/mediate) to assess the mediated proportions of the metabolic factors on the association between long-term O_3 exposure and CVD mortality.[40] According to the existing evidence,[16–19] we selected five metabolic factors, including diabetes, hypertension, dyslipidaemia, general obesity, and abdominal obesity, as the potential mediators (presented as the DAG in Supplementary Methods). Before conducting the mediation analyses, we used logistic regression and Cox proportional hazards models to evaluate the significant association between long-term O_3 exposure and these metabolic factors, as well as to determine if these metabolic factors remain significantly associated with

CVD mortality, respectively (Supplementary Table S2). The mediating proportion by the potential mediators was presented, if it existed. The direct and indirect effects in our study are natural effects according to the previous study.[35] Specially, direct and total effects for each metabolic factor were estimated as a combination of the regression coefficients obtained from the outcome models, with adjustments for confounders represented in the DAG. The indirect effect was then estimated by calculating the difference between the regression coefficients of the total and direct effects. To improve asymptotic behavior, we transform using Fisher's z transformation and the delta method to obtain the 95% confidence limits of the transformed variable, then back-transform to report the 95% CI on the original scale. Furthermore, subgroup analyses were conducted to explore potential variations in the association between long-term O_3 exposure and CVD, IHD, IS, and HS mortality based on age (<65 or ≥65 years), sex (male or female), urbanity (urban or rural), current smoking status (yes or no), occupation (farmer or other), and education level (low or high). To investigate whether the association of long-term O_3 exposure with CVD, IHD, IS, and HS mortality is modified by these subgroups, we added the product terms to the original Cox models to assess the multiplicative interaction (treating the O_3 concentrations as a continuous variable). Subsequently, we classified five-year average O_3 into low and high levels with a cut-point at the median value to further assess the heterogeneity between CVD mortality and subgroups based on additive interaction and multiplicative interaction.[41] Several sensitivity analyses were conducted to assess the robustness of the main findings. First, we excluded participants who died within the first year of follow-up to reduce the potential reverse causation bias. Second, we expanded the exposure time window for O_3 from an average of five years before baseline to the year of enrollment or shortened it to 1, 2, or 3 years before baseline to examine the association between long-term O_3 exposure and outcomes. Third, to further adjust for physical activity and diet patterns (Supplementary Method), we repeated the analysis in a sub-cohort of participants with more comprehensive baseline data. Fourth, we assigned the five-year average warm-season ozone exposure (May to October) as long-term O_3 exposure. Finally, we considered non-CVD death as a competing risk in the proportional sub-hazards model by Fine and Gray.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $P < 0.05$ was considered statistically significant.

Ethics

The project was approved by the central ethics committee at the China National Center for Cardiovascular Diseases (approval no. 2014-574). All registered participants provided written informed consent.

Role of the funding source

The funders had no role in study design, data collection, data analysis, interpretation or writing the manuscript.

Results

Participants characteristics

The baseline characteristics of the included participants by quartiles of O_3 concentrations are presented in Table 1. Among the 3,206,871 included participants, the overall mean age was 55.8 ± 9.9 years, 1,919,478 (59.9%) were female, and 60.0% resided in the rural areas. Of all the participants, 22.4% had high a school or above level, 17.3% had an annual household income over 50,000 yuan, 19.9% and 15.9% were current smokers and alcohol consumers, respectively, and approximately one-half were farmers. Regarding medical history, the proportion of participants with hypertension, diabetes, and dyslipidemia was 46.9%, 7.4%, and 44.2%, respectively (Table 1).

The baseline O_3 concentrations ranged from 60.85 μg/m^3 to 109.79 μg/m^3, with a median (IQR) of 86.82 (81.12–93.82) μg/m^3. Participants with higher O_3 exposure were more likely to reside in urban areas, but less likely to be current smokers or alcohol consumers (all P for trend <0.0001). Moreover, participants with higher O_3 exposure were more likely to have hypertension, diabetes, and dyslipidemia ($P < 0.0001$). Additionally, significant increasing trends were observed in systolic BP, diastolic BP, BMI, and TG with the increase of O_3 levels, while a negative correlation between HDL and O_3 exposure was found.

Association of O_3 exposure with outcomes

During a median follow-up of 4.7 (IQR: 3.7–6.2) years, 35,553 (1.1%) of 3,206,871 participants died from CVD, of whom 13,356 (37.6%) died from IHD, 4755 (13.4%) died from IS, and 7326 (20.6%) died from HS.

In the multivariable-adjusted model, each 10.0 μg/m^3 increment for O_3 was associated with higher risks of mortality from CVD (HR: 1.031, 95% CI: 1.013–1.049), IHD (HR: 1.113, 95% CI: 1.082–1.146), and IS (HR: 1.068, 95% CI: 1.017–1.121) (Table 2). The association between long-term O_3 exposure and HS mortality tended to be null (HR: 0.990, 95% CI: 0.951–1.029). Compared with participants in Q1 of O_3, an increasing trend in HR from Q2 to Q4 for CVD, IHD, and IS mortality. Additionally, individuals exposed to Q4 had the highest HR (95% CI) for CVD mortality: 1.042 (1.003–1.083); IHD mortality: 1.193 (1.120–1.270); and IS mortality: 1.120 (1.007–1.247) (Table 2).

The exposure-response curves for the associations of O_3 with mortality from CVD, IHD, IS and HS, were depicted in Fig. 1, showing a consistent trend between the one-pollutant model and two-pollutant model. A nonlinear relationship between long-term O_3 exposure and mortality due to CVD and IHD was observed in the

Annual average concentration of O_3, μg/m^3	Aggregate	Quartile 1 (%) (~81.12)	Quartile 2 (%) (81.12–86.82)	Quartile 3 (%) (86.82–93.82)	Quartile 4 (%) (93.82~)	*P*-value
N	3,206,871	793,887	806,775	805,684	800,525	–
Age, years	55.84 ± 9.88	55.45 ± 10.01	55.91 ± 9.84	55.69 ± 9.87	56.29 ± 9.79	<0.0001
Sex	–	–	–	–	–	<0.0001
Male	1,287,393 (40.1)	319,095 (40.2)	316,398 (39.2)	327,796 (40.7)	324,104 (40.5)	–
Female	1,919,478 (59.9)	474,792 (59.8)	490,377 (60.8)	477,888 (59.3)	476,421 (59.5)	–
Urbanity	–	–	–	–	–	<0.0001
Urban	1,282,789 (40.0)	333,335 (42.0)	297,160 (36.8)	279,781 (34.7)	372,513 (46.5)	–
Rural	1,924,082 (60.0)	460,552 (58.0)	509,615 (63.2)	525,903 (65.3)	428,012 (53.5)	–
Education	–	–	–	–	–	<0.0001
Primary school or lower	1,399,763 (43.7)	356,700 (44.9)	377,377 (46.8)	326,409 (40.5)	339,277 (42.4)	–
Middle school	1,048,116 (32.7)	241,665 (30.4)	244,764 (30.3)	279,258 (34.7)	282,429 (35.3)	–
High school	475,796 (14.8)	115,716 (14.6)	115,708 (14.3)	129,168 (16.0)	115,204 (14.4)	–
College or higher	243,360 (7.6)	64,052 (8.1)	58,454 (7.3)	61,976 (7.7)	58,878 (7.4)	–
Unknown	39,836 (1.2)	15,754 (2.0)	10,472 (1.3)	8873 (1.1)	4737 (0.6)	–
Lifestyle characteristics	–	–	–	–	–	–
Current smoking	639,463 (19.9)	159,786 (20.1)	160,128 (19.9)	164,209 (20.4)	155,340 (19.4)	<0.0001
Alcohol consumption	510,269 (15.9)	132,299 (16.7)	132,514 (16.4)	123,519 (15.3)	121,937 (15.2)	<0.0001
Occupation	–	–	–	–	–	<0.0001
Farmer	1,567,325 (48.9)	373,871 (47.1)	377,885 (46.8)	410,940 (51.0)	404,629 (50.6)	–
Others	1,639,546 (51.1)	420,016 (52.9)	428,890 (53.2)	394,744 (49.0)	395,896 (49.5)	–
Annual household income, yuan per year	–	–	–	–	–	<0.0001
<10,000	571,424 (17.8)	142,491 (18.0)	131,398 (16.3)	160,850 (20.0)	136,685 (17.1)	–
10,000–50,000	1,775,934 (55.4)	426,093 (53.7)	473,964 (58.8)	452,680 (56.2)	423,197 (52.9)	–
>50,000	555,011 (17.3)	124,845 (15.7)	124,826 (15.5)	121,192 (15.0)	184,148 (23.0)	–
Unknown	304,502 (9.5)	100,458 (12.7)	76,587 (9.5)	70,962 (8.8)	56,495 (7.1)	–
Medical history	–	–	–	–	–	–
Hypertension	1,503,332 (46.9)	340,725 (42.9)	366,525 (45.4)	387,517 (48.1)	408,565 (51.0)	<0.0001
Diabetes mellitus	235,982 (7.4)	49,954 (6.3)	54,454 (6.8)	59,979 (7.4)	71,595 (8.9)	<0.0001
Dyslipidemia	1,417,912 (44.2)	346,651 (43.7)	351,896 (43.6)	353,823 (43.9)	365,542 (45.7)	<0.0001
Metabolic factors	–	–	–	–	–	–
Systolic BP, mmHg	135.80 ± 20.17	134.38 ± 20.65	135.29 ± 20.33	136.21 ± 20.08	137.29 ± 19.51	<0.0001
Diastolic BP, mmHg	81.10 ± 11.24	80.39 ± 11.50	80.92 ± 11.42	81.47 ± 11.09	81.61 ± 10.89	<0.0001
BMI, kg/m^2	24.76 ± 3.42	24.39 ± 3.37	24.42 ± 3.37	24.95 ± 3.40	25.28 ± 3.45	<0.0001
WC, cm	83.93 ± 9.72	83.02 ± 9.55	82.91 ± 9.55	84.28 ± 9.61	85.53 ± 9.92	<0.0001
TC, mmol/L	4.57 ± 1.11	4.64 ± 1.14	4.68 ± 1.10	4.51 ± 1.09	4.46 ± 1.10	<0.0001
TG, mmol/L	1.34 (0.98–1.94)	1.33 (0.97–1.93)	1.33 (0.96–1.94)	1.36 (0.99–1.94)	1.36 (0.98–1.96)	<0.0001
LDL, mmol/L	2.45 ± 1.08	2.47 ± 0.99	2.52 ± 0.95	2.43 ± 1.37	2.40 ± 0.95	<0.0001
HDL, mmol/L	1.44 ± 0.42	1.48 ± 0.44	1.46 ± 0.42	1.42 ± 0.41	1.39 ± 0.40	<0.0001

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table 1: **Baseline characteristics of study participants.**

RCS. However, a linear association was found between IS mortality and long-term O_3 exposure, but the association was not significant for HS mortality. Inflection points were identified at 85.44 μg/m^3 for CVD mortality and 88.15 μg/m^3 for IHD mortality in the two-pollutant model. Subsequently, we applied a Cox proportional hazards model combined with a two-piecewise Cox proportional hazards model based on the inflection points to investigate the nonlinear relationship between long-term O_3 exposure and CVD and IHD mortality (Table 3). When O_3 concentrations exceeded the inflection points, a 10.0 μg/m^3 increase in the O_3 level was associated with a 13.9% and 25.0% greater mortality risk of CVD (HR: 1.139, 95% CI: 1.096–1.184) and IHD (HR: 1.250, 95% CI: 1.151–1.357) mortality, respectively. Conversely, when O_3 levels were below the specific inflection points, the HRs (95% CIs) for CVD and IHD mortality of per 10.0 μg/m^3 increase in the O_3 were 0.991 (0.946–1.038) and 1.040 (0.976–1.108), respectively, which might suggest limited clinical importance

on CVD mortality for the relatively low-level O_3 exposure.

The results of stratified analyses for CVD mortality are presented in Fig. 2. A multiplicative interaction was observed between long-term O_3 exposure and age, smoking, occupation, and education subgroups (all *P* for interaction <0.05), while there were no statistical interactions between long-term O_3 exposure and sex, and urbanity subgroups. Supplementary Table S3 depicts the modification of the influence of high-level O_3 exposure on CVD mortality by the subgroups. High education level and high-level O_3 exposure had a highly negative interaction on the additive (relative excess risk due to interaction [RERI]: –0.053, 95% CI: –0.098 to –0.009). No multiplicative interactions between age, sex, smoking, urbanity, occupation, and education subgroups and O_3 exposure were found (all $P > 0.05$). Taking together, these results further indicate that those had low educational levels may be more susceptible to high-level O_3 exposure. Additionally, the results of stratified analyses for IHD, IS, and HS mortality are shown in Supplementary Figures S2–S4.

In the sensitivity analyses, similar results were found when participants who died in the first year of follow-up were excluded (Supplementary Table S4). Expanding (average O_3 concentrations from five years before baseline to the enrolled year) or shortening (1, 2, or 3 years before baseline) the exposure time window of O_3 yields associations consistent with the main findings (Supplementary Tables S5–S8). The results showed a similar trend when physical activity and diet patterns were further adjusted in a sub-cohort of participants (Supplementary Table S9). Additionally, the major results did not appreciably change in the analysis using the five-year average warm-season ozone exposure (May–October) as long-term O_3 exposure (Supplementary Table S10) and the analysis based on the Fine–Gray models considering non-CVD death (49,916 cases) as a competing risk (Supplementary Table S11).

Outcomes	Ozone alone	*P* value	Ozone adjusted for $PM_{2.5}$	
	HR (95% CI)		HR (95% CI)	*P* value
CVD mortality	–	–	–	–
Per 10 μg/m^3	1.033 (1.016–1.051)	0.0002	1.031 (1.013–1.049)	0.0008
Q1	1 (ref)	–	1 (ref)	–
Q2	0.926 (0.898–0.955)	0.0001	0.898 (0.871–0.926)	<0.0001
Q3	0.972 (0.941–1.005)	0.096	0.967 (0.924–1.001)	0.054
Q4	1.068 (1.030–1.108)	0.0004	1.042 (1.003–1.083)	0.036
IHD mortality	–	–	–	–
Per 10 μg/m^3	1.110 (1.080–1.142)	<0.0001	1.113 (1.082–1.146)	<0.0001
Q1	1 (ref)	–	1 (ref)	–
Q2	0.976 (0.927–1.028)	0.37	0.941 (0.893–0.992)	0.023
Q3	1.020 (0.966–1.077)	0.48	1.014 (0.958–1.073)	0.64
Q4	1.221 (1.150–1.297)	<0.0001	1.193 (1.120–1.270)	<0.0001
IS mortality	–	–	–	–
Per 10 μg/m^3	1.068 (1.019–1.119)	0.0057	1.068 (1.017–1.121)	0.0080
Q1	1 (ref)	–	1 (ref)	–
Q2	1.020 (0.939–1.107)	0.64	0.989 (0.909–1.075)	0.79
Q3	1.061 (0.969–1.161)	0.20	1.060 (0.965–1.164)	0.23
Q4	1.139 (1.029–1.260)	0.012	1.120 (1.007–1.247)	0.037
HS mortality	–	–	–	–
Per 10 μg/m^3	1.005 (0.967–1.044)	0.81	0.990 (0.951–1.029)	0.60
Q1	1 (ref)	–	1 (ref)	–
Q2	0.898 (0.841–0.959)	0.0013	0.875 (0.818–0.936)	<0.0001
Q3	1.058 (0.986–1.136)	0.12	1.029 (0.956–1.108)	0.45
Q4	0.986 (0.908–1.071)	0.74	0.950 (0.871–1.036)	0.25

Adjusted variables included age, sex, urbanity, region, season, income, occupation, education, marital status, temperature, humidity, and elevation. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HS, Hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; $PM_{2.5}$, fine particulate matter; Ref, reference.

Table 2: **Associations between five-year average ozone exposure and CVD mortality.**

Mediation analyses

The mediation analyses revealed that these metabolic factors (i.e., diabetes, hypertension, dyslipidemia, general obesity, and abdominal obesity) significantly contributed to the relationships between long-term O_3 exposure and CVD mortality, including its subcategories (Table 4). For CVD mortality, the mediation proportion by diabetes mellitus was 22.6% (95% CI: 11.0%–41.0%), by hypertension was 16.3% (95% CI: 7.9%–30.5%), by dyslipidemia was 5.3% (95% CI: 2.6%–10.5%), by general obesity was 7.5% (95% CI: 3.7%–14.6%), and by abdominal obesity was 8.9% (95% CI: 4.4%–17.2%). Regarding IHD mortality, the mediation proportions by diabetes, hypertension, dyslipidemia, obesity, and abdominal obesity were 6.5% (95% CI: 4.8%–8.9%), 2.9% (95% CI: 2.0%–4.0%), 1.7% (95% CI: 1.2%–2.5%), 2.1% (1.5%–3.2%), and 2.5% (95% CI: 1.8%–3.7%), respectively. Additionally, the proportions mediated by the five metabolic factors were 12.5% (95% CI: 5.5%–25.8%), 7.7% (95% CI: 3.4%–16.6%), 2.4% (95% CI: 1.0%–5.7%), 2.5% (0.9%–7.2%), and 3.9% (95% CI: 1.5%–9.8%) for IS mortality.

Discussion

In this nationwide large-scale cohort of Chinese adults, we observed nonlinear relationships between long-term O_3 exposure and mortality due to CVD and IHD across a broad exposure range of O_3, with a 13.9% to 25.0% increase in the risk of mortality per 10.0 μg/m^3 increment in O_3 concentrations exceeding the specific inflection points around 87 μg/m^3. The detrimental impacts of O_3 on CVD mortality were more pronounced among participants aged 65 years or older, those residing in rural areas and having low educational levels, and farmers. Furthermore, diabetes, hypertension, dyslipidemia, general obesity, and abdominal obesity mediated more than half of the association between O_3 exposure and CVD mortality.

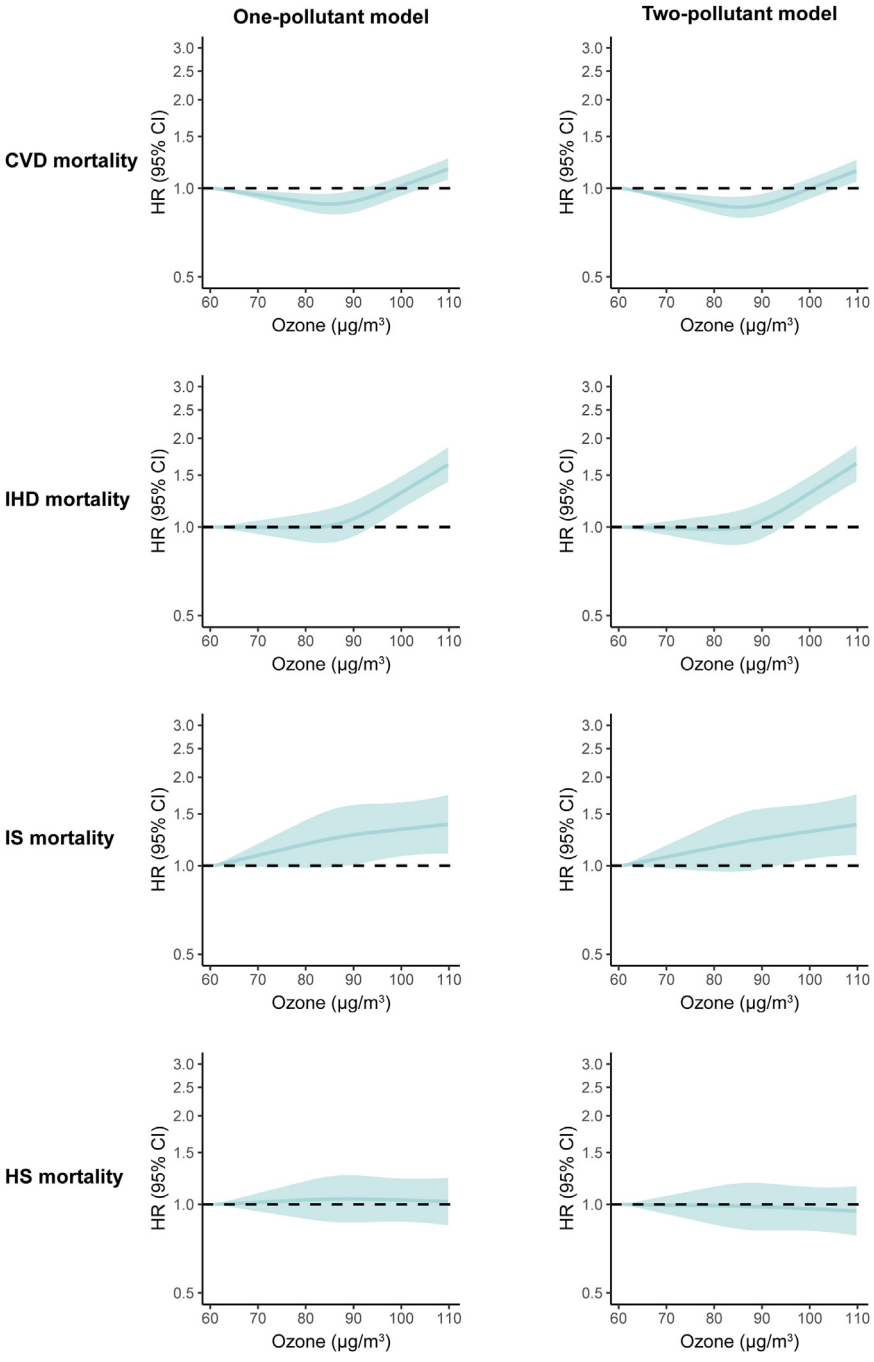

Fig. 1: **Concentration-response association between ozone and CVD mortality**. The solid green lines indicate the hazard function, and the shaded areas represent 95% CIs. One-pollutant model adjusted age, sex, urbanity, region, season, income, occupation, education, marital status, temperature, elevation, and humidity. Two-pollutant model further adjusted $PM_{2.5}$. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HS, Hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; $PM_{2.5}$, fine particulate matter.

Our robust findings have substantially deepened our understanding of the influences of chronic O_3 exposure on CVD mortality. Previous cohort studies, such as those focusing on the general population and teachers in California, did not identify an elevated risk of CVD mortality associated with long-term O_3 exposure,[22,42] likely due to their limited geographical coverage. Similarly, several European cohort studies reported a

Outcomes	Ozone alone	*P* value	Outcomes	Ozone adjusted for $PM_{2.5}$	
	HR (95% CI)			HR (95% CI)	*P* value
CVD mortality	–	–	**CVD mortality**	–	–
Inflection point	84.95 μg/m^3	–	Inflection point	85.44 μg/m^3	–
O_3 <84.95 μg/m^3	0.992 (0.947–1.039)	0.73	O_3 <85.44 μg/m^3	0.991 (0.946–1.038)	0.21
O_3 ≥84.95 μg/m^3	1.135 (1.093–1.178)	<0.0001	O_3 ≥85.44 μg/m^3	1.139 (1.096–1.184)	<0.0001
P for log-likelihood ratio	<0.0001	–	*P* for log-likelihood ratio	<0.0001	–
IHD mortality	–	–	**IHD mortality**	–	–
Inflection point	86.43 μg/m^3	–	Inflection point	88.15 μg/m^3	–
O_3 <86.43 μg/m^3	1.074 (0.999–1.153)	0.051	O_3 <88.15 μg/m^3	1.040 (0.976–1.108)	0.22
O_3 ≥86.43 μg/m^3	1.241 (1.163–1.324)	<0.0001	O_3 ≥88.15 μg/m^3	1.250 (1.151–1.357)	<0.0001
P for log-likelihood ratio	<0.0001	–	*P* for log-likelihood ratio	<0.0001	–

Adjusted variables included age, sex, urbanity, region, season, income, occupation, education, marital status, temperature, humidity, and elevation. CVD, cardiovascular disease; HR, hazard ratio; HS, Hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; O_3, ozone; $PM_{2.5}$, fine particulate matter.

Table 3: **Threshold analysis of long-term ozone exposure (per 10.0 μg/m^3 increase) on CVD mortality.**

negative association between long-term O_3 exposure and CVD mortality across a narrow exposure range of O_3 generally below 40 ppb.[11,12,25] However, these studies often simply attribute this finding to the negative correlation between O_3 and other pollutants, without delving into a comprehensive discussion of the counterintuitive results regarding O_3. In contrast, three cohort studies conducted in the United States and Canada,[10,14,43] revealed a significantly positive, albeit nonlinear association between long-term O_3 exposure

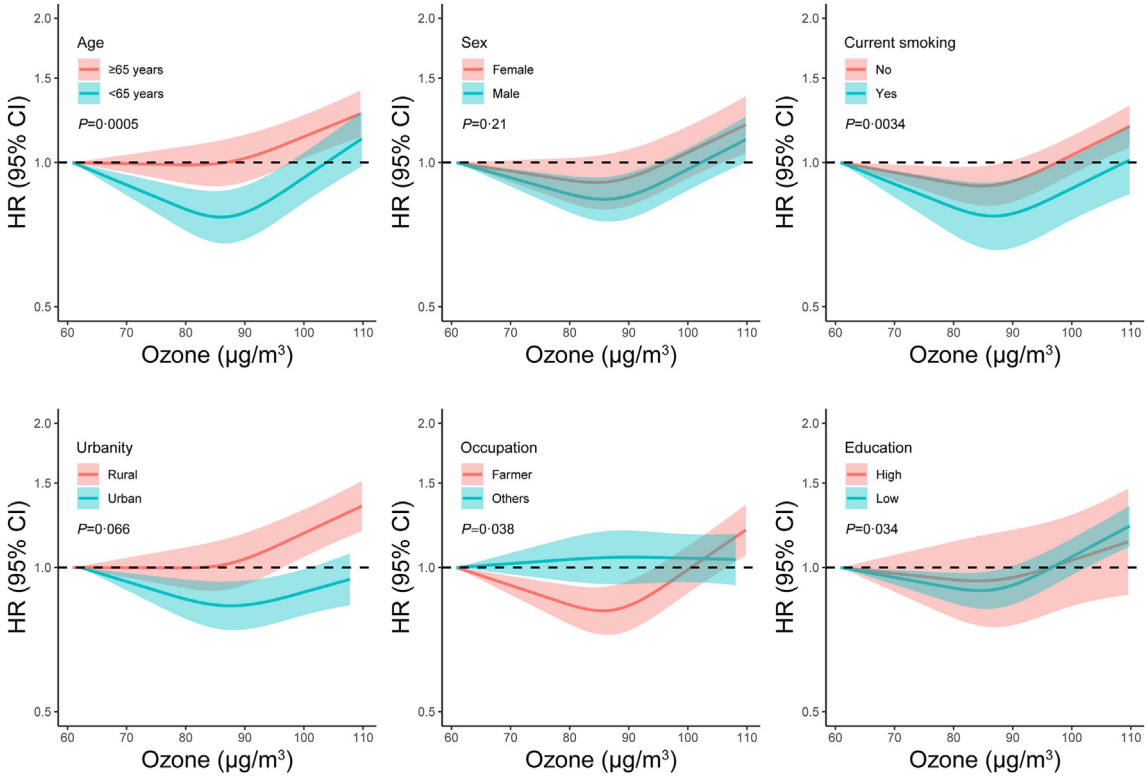

Fig. 2: **Concentration-response association between ozone and CVD mortality in different subgroups in two-pollutant models**. The solid green or red lines indicate the hazard function, and the shaded areas represent 95% CIs. Adjusted age, sex, urbanity, region, season, income, occupation, education, marital status, temperature, elevation, humidity, and $PM_{2.5}$. High education was defined as high school or above, and low education was defined as middle school or below. *P* values were calculated by adding the product items to the original Cox models (treating the O_3 concentrations as a continuous variable).

Mediators	Ozone alone		Ozone adjusted for $PM_{2.5}$	
	Proportion of effect mediated by mediator (%)	*P* value	Proportion of effect mediated by mediator (%)	*P* value
CVD mortality	–	–	–	–
Diabetes	17.86 (9.48–31.11)	<0.0001	22.63 (10.96–41.01)	<0.0001
HTN	15.81 (8.36–27.87)	<0.0001	16.27 (7.93–30.49)	<0.0001
Dyslipidemia	3.73 (1.96–6.98)	<0.0001	5.30 (2.61–10.45)	<0.0001
Obesity	8.59 (4.54–15.67)	<0.0001	7.45 (3.66–14.56)	<0.0001
Abdominal obesity	9.28 (4.95–16.73)	<0.0001	8.93 (4.42–17.21)	<0.0001
IHD mortality	–	–	–	–
Diabetes	5.64 (4.11–7.68)	<0.0001	6.54 (4.80–8.86)	<0.0001
HTN	2.80 (1.99–3.92)	<0.0001	2.85 (2.02–4.00)	<0.0001
Dyslipidemia	1.24 (0.83–1.85)	<0.0001	1.72 (1.19–2.47)	<0.0001
Obesity	2.70 (1.84–3.94)	<0.0001	2.14 (1.45–3.16)	<0.0001
Abdominal obesity	2.83 (1.98–4.05)	<0.0001	2.54 (1.75–3.66)	<0.0001
IS mortality	–	–	–	–
Diabetes	10.62 (4.84–21.73)	<0.0001	12.47 (5.50–25.83)	<0.0001
HTN	8.40 (3.79–17.58)	<0.0001	7.67 (3.36–16.57)	<0.0001
Dyslipidemia	1.86 (0.80–4.27)	<0.0001	2.43 (1.02–5.69)	<0.0001
Obesity	3.17 (1.12–8.67)	0.0025	2.53 (0.86–7.20)	0.0035
Abdominal obesity	4.40 (1.77–10.54)	<0.0001	3.94 (1.53–9.75)	<0.0001

Adjusted variables included age, sex, urbanity, region, smoking, alcohol consumption, season, income, occupation, education, medical insurance, marital status, temperature, humidity, and elevation. CVD, cardiovascular disease; HS, Hemorrhagic stroke; HTN, hypertension; IHD, ischemic heart disease; IS, ischemic stroke; $PM_{2.5}$, fine particulate matter.

Table 4: **Mediation analysis of the ozone on the CVD mortality by risk factors.**

and CVD mortality. Notably, according to the exposure-response curves, the thresholds for CVD mortality were 35 and 40 ppb in the two US cohort study, respectively,[10,14] being consistent with our results. However, it's important to note that these studies only estimated the overall effect assuming linearity even if the nonlinear exposure-response relationship exists, which might significantly underestimate the health effects of O_3 on CVD mortality. In contrast, we fitted a two-segment Cox proportional risk model based on the shapes of RCS to identify the inflection points and fully adjusted for potential confounders, including comprehensive socioeconomic, behavioral, and environmental characteristics. Our analysis revealed a positive association between O_3 exposure and CVD mortality only when the O_3 concentrations exceeded 85.44 $\mu g/m^3$. Thus, taken together, the inconsistent findings across studies may be attributed to various factors, such as the range of O_3 exposure, the accuracy of the statistical model, the size and geographical coverage of the samples, and population susceptibility.

Heterogeneities in the association between O_3 exposure and overall and cause-specific CVD mortality imply vulnerability of specific subpopulations. In accordance with our findings, two cohort studies also reported higher risk estimates of CVD mortality among the elderly,[14,21] which may be explained by the fact that the elder individuals who typically experience more metabolic disorders and poorer lung function, tend to be sensitive to O_3 exposure.[44] Furthermore, farmers and individuals with lower education levels had a higher risk of CVD mortality, possibly due to longer hours of outdoor labor than others. A recent study reported a slightly higher CVD mortality risk associated with O_3 exposure among females, although the difference was not statistically significant.[45] Our findings show that such an association is significantly and consistently higher among females for IHD mortality, which may be attributed to morphological differences in the respiratory system between the sexes.[46] More importantly, the observed additive interaction indicates that the public health consequences of low education levels would be greater in individuals with high-level O_3 exposure.

The mediation proportions of metabolic risk factors exceed one-half, indicating potential targets for alleviating the disease burden. Several studies have suggested that metabolic diseases, such as hypertension, diabetes, dyslipidemia, and obesity, which are well-established risk factors for CVD, may be caused by ambient O_3 pollution,[16–19] implying that O_3 may indirectly contribute to CVD mortality. Among these selected five risk factors, hypertension and diabetes emerge as the two primary mediators for CVD mortality, primarily driving the IS mortality. Previous findings also consistently suggest that hypertension has the largest population-attributable fractions for CVD mortality, followed closely by diabetes.[47] Although the exact biological mechanisms underlying these metabolic risk factors on how long-term O_3 exposure contributes to CVD mortality are not fully understood, several plausible explanations have been proposed. For example, oxidative stress and dysfunction of the autonomic nervous system and neuroendocrine system triggered by O_3 may lead to systematic inflammation.[48–50] Subsequently, inflammatory cytokines could further impair the vascular endothelium, activate platelets, and ultimately increase blood coagulation and blood pressure.[51–53] In addition, these processes may contribute to insulin resistance and metabolic disorders in lipid profiles,[54,55] and eventually result in obesity, diabetes, and dyslipidemia.

Given the impacts of O_3 on CVD mortality, its disease burden has been dramatically underestimated, which has major policy implications. First, comprehensively assessing the health hazards of O_3 is crucial for establishing air quality guidelines (AQG). The current estimates of disease burden attributable to ambient O_3 pollution in both the Global Burden of Disease study and the World Health Organization's published AQG only consider the effects of O_3 exposure on all-cause mortality from chronic obstructive pulmonary disease in developed counties.[2,56] However, the excess risk of CVD mortality suggests that additional disease burden needs to be considered. It is time to implement more rigorous air pollution control standards or regulations,

especially in developing countries where AQG is inadequate or even lacking, and air quality is often worse. Second, although short-term (8-h) daily maximum and peak season AQG levels for O_3 have been recommended, evidence on the annual AQG level is scarce. Therefore, there is an urgent necessity to examine the chronic effect of O_3 exposure on CVD mortality across a broad exposure range of O_3 to better understand the health effects of O_3 on the cardiovascular system and provide fresh evidence for more accurate estimations of disease burden. Third, individual exposure protection measures for O_3 should be implemented. Spending more time indoors, opting for less strenuous outdoor activities, and planning outdoor activities in the morning or evening, particularly for vulnerable populations when ground-level O_3 levels are high, are recommended by the United States Centers for Disease Control and Prevention's Ozone and Your Health.[57] Finally, considering that metabolic factors mediate a considerable proportion of O_3-caused CVD mortality, there is an urgent need for governments to implement targeted policies and interventions aimed at lowering the prevalence of diabetes, hypertension, dyslipidemias, general obesity, and abdominal obesity.

Despite the strengths outlined above, several limitations should be acknowledged. First, we estimated the individuals' O_3 exposure by linking their residential address at baseline to ambient O_3 concentrations, which may lead to exposure misclassification due to limited time spent outdoors and potential relocation during the study period. Second, although we adjusted for various potential confounders based on the DAG in the Cox models, unmeasured confounding, like other ambient pollutants nitrogen dioxide, and black carbon, and residual confounding due to measurement errors in confounders such as income, smoking, and alcohol consumption, could confound the association between chronic O_3 exposure and CVD mortality.[9,23] Therefore, the potential confounding effects of other ambient pollutants and residual confounding should be fully considered in future research. Third, although a mandatory death registration system has been well established, a small proportion of missing death records may exist, potentially underestimating the influences of O_3. Fourth, given that this is an observational study, the causal roles of metabolic mediators in the association between O_3 and CVD mortality could not be established. Nevertheless, we used the average ozone exposure over the five years preceding the baseline measurements, with mortality events occurring after these baseline factors, to establish a sound temporal sequence. Moreover, reverse causations are unlikely to exist between ozone and metabolic indicators, or metabolic indicators and mortality. Fifth, the potential for selection bias associated with the use of HRs should be noted. As highlighted by Hernán (2010),[58] HRs can be influenced by various factors, including differential loss to follow-up and time-varying covariates, which may affect the interpretation of the results. Additionally, since our results are based on a two-tailed $P < 0.05$ threshold for statistical significance, it is essential to consider the uncertainties in estimates when interpreting our findings.[59,60] Finally, our cohort study was not established using a random sampling design and had a low response rate, which may introduce selective bias.

Our study identified a nonlinear relationship between long-term O_3 exposure and mortality from CVD and IHD across a broad exposure range of O_3. This finding may, to some extent, respond to the inconsistency of previous studies on the relationship between O_3 and CVD mortality. Improving metabolic factors in individuals exposed to relatively high levels of O_3, particularly among those aged 65 years and older, females, non-smokers, farmers, and those with relatively low-level education, could be an effective strategy to mitigate the detriments of O_3 on health. Our findings contribute to refining more accurate estimations of disease burden and inform the development of ozone pollution standards.

Contributors

Study concept and design: Zenglei Zhang, Chunqi Wang, Chunying Lin, Xianliang Zhou, and Xi Li. Acquisition of data: Zenglei Zhang, Chunqi Wang, Chunying Lin, Yi Wu, Jing Wei, Jiapeng Lu, Bowang Chen, Chaoqun Wu, Xiaoyan Zhang, Yang Yang, Jianlan Cui, Wei Xu, Lijuan Song, Hao Yang, Yan Zhang, Wenyan He, Yuan Tian, and Xi Li. Statistical analysis and data visualisation: Yi Wu, Chunying Lin, and Zenglei Zhang. Data interpretation: Zenglei Zhang, Chunqi Wang, Chunying Lin, Xianliang Zhou, and Xi Li. Manuscript preparation: Zenglei Zhang, Chunqi Wang, and Xi Li. Critical revision of the manuscript: Zenglei Zhang, Chunqi Wang, Chunying Lin, Jing Wei, Jianlan Cui, Xianliang Zhou, and Xi Li. Supervision: Xianliang Zhou, and Xi Li. Funding acquisition: Xi Li. Zenglei Zhang, Chunqi Wang, Chunying Lin, Yi Wu, and Xi Li had full access to all the data in the study. All authors read and approved the final manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author Xi Li (xi.li@nccd.org.cn), upon reasonable request.

Declaration of interests

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101222.

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