Comment Letter #85

From: Osterman, Gregory B (US 329I) <gregory.b.osterman@jpl.nasa.gov>
Sent: Saturday, August 13, 2022 2:44 PM
To: Sang-Mi Lee <slee@aqmd.gov>
Subject: Air Quality and Health Appendix - Comments

Hi Sang-Mi,

I apologize for this being late. I did go through the Air Quality and Health appendix, though I focused mostly on the ozone sections. The document looks to be very thorough, with an impressive amount of referenced support for the need to help alleviate the effects of air quality on human health.

I did not ask any questions during the meeting, I felt my questions were asked by other members of the committee and answered during the meeting. My questions had to do with the ISA, which I was not too familiar with. The relationships in table I-2 seem to be very conservative when describing the risks to health from ozone exposure, but now I understand that they are defined by the EPA. The case for the effects of ozone on health is still overwhelmingly made in the document.

Also I know that the team that wrote the appendix had to stop at some point and could not consider the most recent papers. I did a quick search and found the attached paper that started with the same premise as table I-2, that the relationship between long-term ozone exposure and cardiovascular mortality has not been established as causal. The findings of the paper seem to support the relationship and add to the evidence that their might be a causal relationship. Maybe the team already saw this paper, I just found it and thought I would pass it along.

Lastly, and this is closer to the subject area I am more familiar with, I did not see any papers from the NASA Health and Air Quality Applied Science Team about air quality and health effects that utilize satellite data. These are more recent papers (publication list here), so maybe they came out after the appendix draft was completed. But there seem to be some papers that might help illustrate the relationships between PM2.5, NO2 or ozone and health. As you know the satellite data has limitations, but is good at looking at larger areas or away from places with surface instrumentation. In particular, Susan Anenberg's group has published some interesting papers (link). The appendix is very thorough, it might not need the satellite papers, but I thought I would point them out.

Again, great job by the SCAQMD team working on the draft AQMP and the health effects appendix in particular.

Best regards,

Greg

Articles

Long-term exposure to ozone and cardiovascular mortality in China: a nationwide cohort study

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Summary

Background The evidence for a causal relationship between long-term ozone exposure and cardiovascular mortality is inconclusive, and most published data are from high-income countries. We aimed to investigate the association between long-term exposure to ozone and cardiovascular mortality in China, the most populous middle-income country.

Methods We did a nationwide cohort study comprising Chinese adults aged 18 years and older from the 2010–11 China Chronic Disease and Risk Factors Surveillance project; participants were followed up until Dec 31, 2018, or the date of death. Data on participants' deaths were obtained through linkage to the Disease Surveillance Point system, a national death registration database. Residential ozone exposure was estimated with a previously developed random forest model. We applied stratified Cox proportional hazards models to estimate the associations of ozone with mortality due to overall cardiovascular diseases, ischaemic heart disease, and stroke. The models were stratified by age and sex and adjusted for a set of individual-level and regional covariates. Warm-season average ozone concentration for the previous 1–3 years was added as a time-varying variable. We also did subgroup analyses by age, sex, level of education, smoking status, urban or rural residence, and geographical region.

Findings Data were analysed for 96 955 participants. The warm-season average ozone concentration during the follow-up period was 89·7 μg/m³ (SD 14·4). In the fully adjusted models, we observed significant and positive associations between ozone and mortality from overall cardiovascular diseases (hazard ratio [HR] 1·093 [95% CI 1·046–1·142] per 10 μg/m³ increase in warm-season ozone concentrations), ischaemic heart disease (1·184 [1·099–1·276] per 10 μg/m³ increase in warm-season ozone concentrations), and stroke (1·063 [1·002– 1·128] per 10 μg/m³ increase in warm-season ozone concentrations). After adjusting for fine particulate matter, the associations with overall cardiovascular disease and ischaemic heart disease mortality were almost unchanged, whereas the association with stroke mortality lost statistical significance. The association of long-term ozone exposure with cardiovascular mortality was more prominent in people aged 65 years and older than in those younger than 65 years. We did not find any effect modification of sex, level of education, smoking status, urban or rural residence, and geographical region. We observed an almost linear exposure–response relationship between ozone and cardiovascular mortality.

Interpretation This study is, to the best of our knowledge, the first nationwide cohort study to show that long-term ozone exposure contributes to elevated risks of cardiovascular mortality, particularly from ischaemic heart disease, in a middle-income setting. The exposure–response function generated from this study could potentially inform future air quality standard revisions and environmental health impact assessments.

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Introduction

Ground-level ozone is a typical secondary air pollutant that is formed by a series of sunlight-driven reactions involving nitrogen oxides and volatile organic compounds. Ground-level ozone pollution is a persistent challenge in high-income countries and is now a growing concern in low-income and middle-income countries as well. In 2019, population-weighted seasonal ozone concentrations in different countries ranged from approximately 20 μg/m³ to 130 μg/m³.[1] Ozone pollution is of particular concern in China, which has a higher population-weighted ozone concentration than most other countries.[2]

According to the findings of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, approximately 0·4 million deaths worldwide were estimated to be attributable to ozone air pollution in 2019.[1] The estimate only relied on the analysis of five large-scale cohorts in high-income countries (eg, Canada, the UK, and the USA),[3] without including any data from low-income and middle-income countries. Given that these exposure–response curves can substantially sway GBD estimates, we believe additional evidence is needed. It is especially pertinent that ozone-related deaths could be underestimated as previous modelling approaches only considered mortality from chronic obstructive pulmonary disease. Other major diseases, such as cardiovascular diseases, have not been included in previous estimates.

The effects of ozone on the cardiovascular system have been extensively investigated in short-term exposure

Research in context

Evidence before this study

We searched PubMed with the MeSH terms "ozone" AND "long-term" AND ("cardiovascular disease" OR "coronary disease" OR "stroke") for all studies published in English from database inception to Dec 31, 2020. We found a few epidemiological studies reporting associations between long-term ozone exposure and mortality due to cardiovascular diseases. However, these studies were mainly done in high-income countries (eg, Canada, the UK, and the USA), and the findings were inconclusive. To date, no nationwide cohort study has investigated such associations in low-income and middle-income countries, whose demographic characteristics, socioeconomic status, and ozone exposure levels are different from those of high-income countries.

Added value of this study

To the best of our knowledge, this is the first nationwide cohort study to investigate the effects of long-term ozone exposure on mortality in a middle-income setting. In this cohort study of 98 058 adults aged 18 years and older in China, we found that long-term ozone exposure was significantly associated with increased risks of mortality due to cardiovascular diseases, especially ischaemic heart disease. Such associations were more prominent in people aged 65 years and older than in those younger than 65 years. Additionally, we observed an almost linear exposure–response curve for the relationship between ozone and cardiovascular mortality.

Implications of all the available evidence

Our findings provide a better understanding of the causal relationship between long-term ozone exposure and cardiovascular diseases, suggesting that a peak-season standard for ambient ozone concentrations, in addition to the current 8 h or 1 h standards, is needed. Furthermore, when combined with the available evidence from the literature, our findings could help to establish a more precise exposure–response function for future estimation of disease burden.

studies.[4,5] However, only a few studies have examined such associations in the context of long-term exposure. Existing evidence for a causal relationship between long-term ozone exposure and cardiovascular mortality, derived from several cohorts in the USA and Europe, was insufficient and inconsistent.[6,7] In this context, the US Environmental Protection Agency stated that there is no conclusive evidence of a causal relationship between long-term ozone exposure and cardiovascular outcomes.[8] In two studies done in the USA, researchers found positive associations between long-term ozone exposure and cardiovascular mortality.[9,10] However, to date, no study has been done in a low-income or middle-income country to support these findings. We aimed to investigate whether long-term ozone exposure was associated with cardiovascular mortality in China and to further explore potential effect modification.

Methods

Study design and population

For this cohort study, we analysed data from participants included in the China Chronic Disease and Risk Factors Surveillance (CCDRFS) project, a cross-sectional survey done in 2010–11. We collected information on participants' deaths through linkage to the Disease Surveillance Point (DSP) system, a national death registration database, until the end of 2018. Details about the CCDRFS project have been published previously;[11] the project was originally designed to understand the prevalence of and risk factors for chronic diseases in China. In the CCDRFS project, participants were randomly selected from 162 study sites across the country. After excluding one study site outside of the DSP system, the remaining 161 sites (97 rural and 64 urban) that were completely covered by the DSP system were included in the present study (appendix p 4). All 161 sites were randomly selected with an iterative method involving multistage stratification to ensure that these sites covered the representative geographical areas of all 31 provinces, autonomous regions, and municipalities in mainland China (figure 1). At each DSP site, a method of multistage stratified cluster random sampling was used to obtain a representative sample of adults aged 18 years and older. Only one person was randomly selected from each sampled household. Further details of sampling are provided in the appendix (p 2).

The study protocol was approved by the ethical review committee of the Chinese Center for Disease Control and Prevention. Written informed consent was obtained from all participants.

Baseline data and follow-up

Individual-level information obtained through face-to-face questionnaire interviews under the 2010–11 CCDRFS project was used as baseline data for this cohort study, including data on personal characteristics, lifestyle risk factors, and medical history. Specifically, educational attainment was classified as elementary school or below, middle school, high school, and above high school. Marital status was categorised as never married, married or cohabiting, divorced or separated or widowed, and other. Participants were grouped according to smoking status and intensity as follows: non-smokers, former smokers, current smokers of one pack or less per day, and current smokers of more than one pack per day. Exercise was classified as high-intensity exercise, medium-intensity exercise, and absence of regular exercise. Information was also collected on passive smoking, alcohol drinking status and intensity, daily consumption of vegetables and fruits, as well as the onset of cardiovascular events in the 12 months before the

See Online for appendix

interview. Additionally, two city-level variables were derived from the China Statistical Yearbook 2011: gross domestic product (GDP) per capita and the number of hospital beds per thousand people.

Each participant was followed up from their enrolment up to Dec 31, 2018, or the date of death through the DSP system, which has been used in various governmental reports and international publications.[12,13] In this study, mortality data from the DSP system were merged with baseline data from the CCDRFS project, relying on the unique identification number of each individual. Deaths were ascertained and coded by trained staff according to the tenth version of the International Classification of Diseases. All death records were reviewed annually, strictly following quality control procedures. For the present analysis, we extracted data on deaths from overall cardiovascular diseases (I00–I99), ischaemic heart disease (I20–I25), and stroke (I60–I69).

Exposure assessment

Ambient ozone concentrations were estimated with a previously developed random forest model at 1 km spatial resolution.[14] In brief, we used the ground-level maximum daily 8 h average (MDA8) ozone measurements in 2013–19 as the dependent variable and used the spatiotemporal predictors during the same period, including Community Multiscale Air Quality simulations, meteorological parameters, elevation, road networks, and population data, as the independent variables to develop the random forest model. Details about these variables can be found in the appendix (pp 2–3) and have also been published previously.[14] The performance of the random forest model was evaluated with cross-validation where training and testing sets were drawn by use of bootstrap sampling. The cross-validated R^2 between predictions and measurements at the monthly level was 0·83, the root-mean-square error (RMSE) was 14·46 μg/m³, and the mean absolute percentage error was 16·62%, indicating a relatively high accuracy of prediction. We used this exposure model and the spatiotemporal predictors in the corresponding years to predict ambient MDA8 ozone concentrations in China between 2005 and 2018. Residential ozone exposure was estimated by assigning the predicted ozone concentrations to each participant's residential address at baseline. In this study, long-term ozone exposure was estimated by calculating an average of MDA8 ozone concentrations during the warm season (May to October).

To adjust for the potential confounding effects of fine particulate matter ($PM_{2·5}$), we estimated $PM_{2·5}$ concentrations at a 1 km spatial resolution following the method described previously.[15] In brief, we used random forest algorithms to develop a gap-filling approach by linking ground-level $PM_{2·5}$ measurements (the dependent variable) to a set of predictors (the independent variables), including simulated $PM_{2·5}$ concentrations from MERRA-2 (Modern-Era Retrospective Analysis for Research and Applications, Version 2), aerosol optical depth product, meteorological parameters, land use, population density, and visibility data. The cross-validated R^2 between $PM_{2·5}$ predictions and measurements at the daily level was 0·81 and RMSE was 18·5 μg/m³.

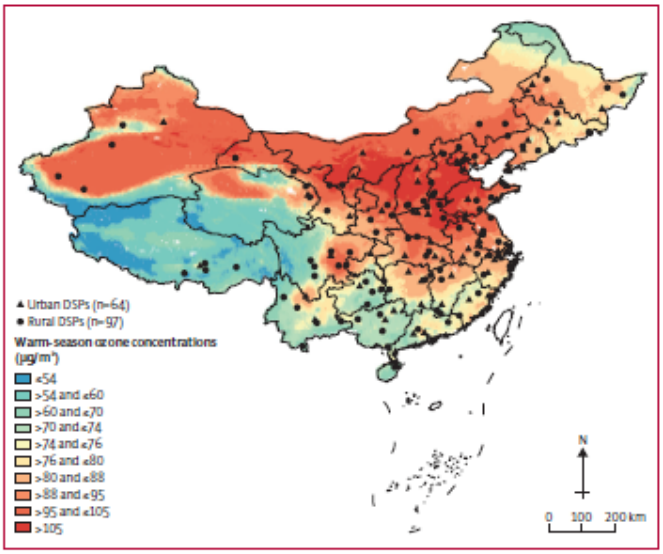

Figure 1: **Spatial variation in warm-season ozone concentrations (May–October, 2010) and location of all 161 sites in the DSP system**
DSP=Disease Surveillance Point.

Statistical analysis

Stratified Cox proportional hazards models were applied to evaluate the effects of ozone on cardiovascular mortality. The proportional hazards assumption for each Cox model was verified with the Schoenfeld residual test, and we detected no violations. We fitted four models (models 1–4). All models were stratified by 1-year age categories and sex to allow for flexible stratum-specific mortality rates at baseline. The covariates in model 1 included body-mass index (BMI), BMI squared, education, marital status, smoking, passive smoking (yes or no), alcohol drinking status (yes or no), consumption of alcohol, and two region-level variables (urban or rural residence and geographical region). In model 2, we further adjusted for two city-level socioeconomic variables (ie, GDP per capita and the number of hospital beds per thousand people). In model 3, we further added three individual-level variables, including consumption of fresh vegetables, consumption of fresh fruits, and exercise. Finally, we fitted model 4 by incorporating two dichotomous variables to model 3 (ie, the onset of stroke and acute myocardial infarction in the previous 12 months) to control for the influence of comorbidity. In all models, long-term ozone exposure was treated as a

	Participants (n=96 955)
Age, years	46·5 (15·0)
Sex	
Female	52 631 (54·3%)
Male	44 324 (45·7%)
Body-mass index, kg/m²	23·9 (3·6)
Educational attainment	
Elementary school or lower	42 303 (43·6%)
Middle school	30 791 (31·7%)
High school	15 823 (16·3%)
Above high school	8038 (8·3%)
Marital status	
Never married	8300 (8·6%)
Married or cohabitating	78 768 (81·2%)
Divorced, separated, or widowed	9680 (10·0%)
Other	207 (0·2%)
Smoking status	
Non-smoker	65 821 (67·9%)
Former smoker	5326 (5·5%)
Current smoker of <1 pack per day	11 090 (11·3%)
Current smoker of >1 pack per day	2875 (3·0%)
Unknown	11 933 (12·3%)
Passive smoking	
No	46 399 (47·9%)
Yes	50 556 (52·1%)
Alcohol drinking status	
No	62 958 (64·9%)
Yes	33 997 (35·1%)
Daily consumption of alcohol, g/day	6·9 (20·9)
Daily intake of vegetables, g/day	330·3 (269·0)
Daily intake of fruits, g/day	85·1 (144·9)
Exercise	
High-intensity exercise	4818 (5·0%)
Medium-intensity exercise	11 327 (11·7%)
Absence of regular exercise	80 810 (83·3%)

Data are mean (SD) or n (%).

Table 1: **Basic characteristics of participants at enrolment**

	Ozone alone	Ozone adjusted for $PM_{2.5}$*
Model 1		
Overall cardiovascular disease	1·094 (1·048–1·142)	1·109 (1·039–1·184)
Ischaemic heart disease	1·174 (1·091–1·264)	1·158 (1·042–1·288)
Stroke	1·064 (1·004–1·128)	1·056 (0·966–1·156)
Model 2		
Overall cardiovascular disease	1·093 (1·046–1·142)	1·110 (1·040–1·186)
Ischaemic heart disease	1·182 (1·097–1·274)	1·169 (1·051–1·301)
Stroke	1·063 (1·002–1·127)	1·057 (0·966–1·158)
Model 3		
Overall cardiovascular disease	1·094 (1·047–1·143)	1·102 (1·032–1·177)
Ischaemic heart disease	1·186 (1·100–1·278)	1·169 (1·050–1·301)
Stroke	1·063 (1·002–1·128)	1·047 (0·955–1·147)
Model 4		
Overall cardiovascular disease	1·093 (1·046–1·142)	1·104 (1·033–1·180)
Ischaemic heart disease	1·184 (1·099–1·276)	1·170 (1·051–1·302)
Stroke	1·063 (1·002–1·128)	1·050 (0·958–1·150)

Data are hazard ratios (95% CIs). Model 1: stratified by age and sex, and adjusted for body mass index (BMI), BMI squared, education, marital status, smoking, passive smoking, alcohol drinking status, consumption of alcohol, urban or rural residence, and geographical region. Model 2: model 1 plus city-level gross domestic product (GDP) per capita plus the number of hospital beds per thousand people. Model 3: model 2 plus daily consumption of vegetables plus daily consumption of fruits plus exercise. Model 4: model 3 plus the onset of stroke and acute myocardial infarction in the 12 months before baseline. * The two-pollutant model was further adjusted for the annual concentrations of fine particulate matter ($PM_{2.5}$) in the year of enrolment.

Table 2: **Associations of cardiovascular mortality with a 10 μg/m³ increase in warm-season ozone concentrations**

time-varying variable at yearly intervals to account for temporal variation in ozone concentrations. To explore lag patterns, we constructed five time-varying exposure variables by calculating the average ozone concentration for each individual and for each follow-up year during the preceding one to five warm seasons. The lag window that generated the largest risk estimate was used in the main analysis. We did not consider exposure during the current year to avoid exposure misclassification due to chronological disorder. Additionally, to test whether the effects of ozone were confounded by long-term $PM_{2.5}$ exposure, we fitted two-pollutant models as in previous studies by adding residential annual concentrations of $PM_{2.5}$ to models 1–4.[9,10]

Based on model 4, we did subgroup analyses by age (<65 years *vs* ≥65 years), sex (male *vs* female), educational attainment (low *vs* high), smoking status (non-smokers *vs* former smokers *vs* current smokers), residential area (urban *vs* rural), and geographical region (north *vs* south). Low educational attainment was defined as elementary school or below, whereas high educational attainment was defined as above elementary school. Between-group differences were tested with the Cochran's Q-test.

Last, to allow for more flexibility in plotting exposure–response curves, we incorporated a penalised spline function of ozone in place of a linear term of ozone in model 4. Four degrees of freedom were automatically set for the penalised splines according to the Akaike Information Criterion. The other variables were the same as those in model 4. The linearity of the curves was examined by comparing the mean square of the residuals between the non-linear models and the corresponding linear models by use of an F-test.[36] A p value greater than 0·05 indicates that there is no significant difference between the two models and therefore the linearity of the curves cannot be denied.

All analyses were done with R software (version 4.0.3). In descriptive analyses, continuous variables were expressed as means with corresponding SDs and categorical variables were expressed as counts with percentages. Effect estimates were presented as hazard ratios (HRs) and their 95% CIs for a mortality outcome associated with a 10 μg/m³ increase in ozone concentrations.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the Article.

Results

98 058 adults from the CCDRFS project were included in our cohort study and were followed up through the DSP system up to Dec 31, 2018, or the date of death (appendix p 4). We included 96 955 participants in the analyses; 1103 participants were excluded due to missing data on baseline variables (appendix p 4). The demographic characteristics of all eligible participants at enrolment are summarised in table 1. All participants were 18 years or older, with an average age of 46·5 (SD 15·0) years. More than half of participants were female and 75·3% were not educated up to high school. During the follow-up period, 2064 (2·1%) of 96 955 participants died from cardiovascular diseases overall, of whom 726 (35·2%) died from ischaemic heart disease and 1116 (54·1%) died from stroke. During the follow-up period, participants' warm-season ozone exposure was 89·7 μg/m³ (SD 14·4) on average, nearly 50% higher than WHO's air quality guidelines (peak season average for ozone of 60·0 μg/m³). The spatial variation of ozone concentrations is shown in figure 1. There was a relatively high correlation (r=0·77) between participants' warm-season ozone exposure and their annual $PM_{2·5}$ exposure.

The lag patterns were similar for the effects on mortality from overall cardiovascular diseases, ischaemic heart disease, and stroke (appendix p 5). The effect estimates increased from lag 1 year to lag 3 years, and then decreased in longer lag times. Therefore, we used the 3-year warm-season average ozone concentrations with a lag of 1–3 years in the subsequent statistical analyses.

We consistently found significant associations between long-term ozone exposure and elevated risks of mortality due to overall cardiovascular diseases (HR 1·093 [95% CI 1·046–1·142] per 10 μg/m³ increase in ozone concentrations), ischaemic heart disease (1·184 [1·099–1·276] per 10 μg/m³ increase in ozone concentrations), and stroke (1·063 [1·002–1·128] per 10 μg/m³ increase in ozone concentrations) in the single-pollutant model 4 (table 2). After adjusting for long-term $PM_{2·5}$ exposure, the associations with mortality due to overall cardiovascular disease and ischaemic heart disease remained almost unchanged. The effect on mortality due to stroke did not change appreciably in magnitude, but the association lost statistical significance with a wider 95% CI. In the two-pollutant model 4, a 10 μg/m³ increase in ozone concentrations was associated with an increase of 10·4% (HR 1·104 [95% CI 1·033–1·180]) in overall cardiovascular disease mortality, 17·0% (1·170 [1·051–1·302]) in ischaemic heart disease mortality, and 5·0% (1·050 [0·958–1·150]) in stroke mortality.

The results of subgroup analyses are shown in figure 2. We found that long-term ozone exposure had a greater effect on cardiovascular mortality in people aged 65 years and older than in those younger than 65 years (p=0·018). The effect on cardiovascular mortality was modestly larger in rural areas and southern China, but the between-group differences did not reach statistical significance. We did not observe significant between-group differences in sex, educational attainment, or smoking status.

The exposure–response curves for the relationships between ozone and mortality from overall cardiovascular diseases, ischaemic heart disease, and stroke are shown in figure 3. Overall, all three exposure–response curves showed a monotonic increasing trend. The slope of the curve for mortality due to ischaemic heart disease was slightly steeper, while the other two curves were flatter. The p values for comparisons between the non-linear and linear models were 0·44 for overall cardiovascular disease mortality, 0·22 for ischaemic heart disease mortality, and 0·53 for stroke mortality, suggesting that all three curves were nearly linear.

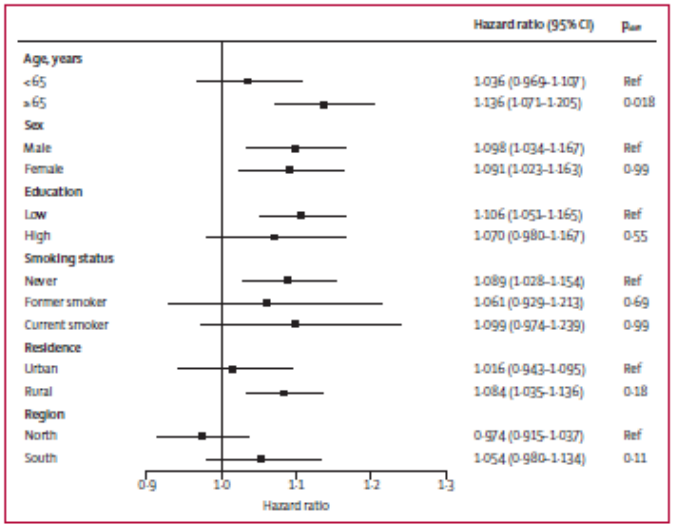

Figure 2: **Associations of cardiovascular mortality with a 10 μg/m³ increase in warm-season ozone concentrations by covariates.**
High education was defined as above elementary school, and low education was defined as elementary school or below. p_{het} values refer to the statistical tests for the between-group differences.

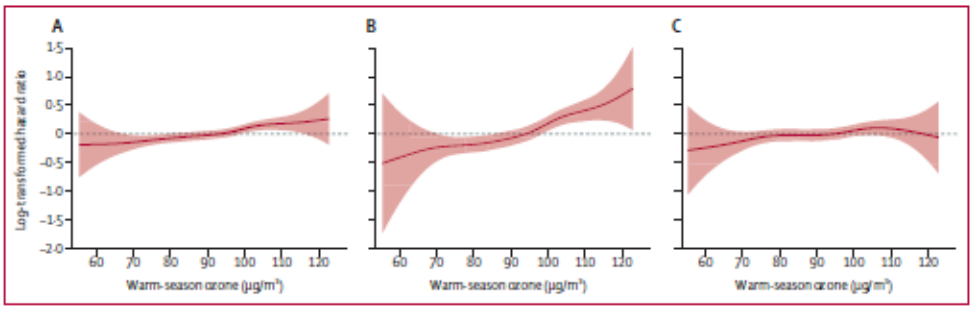

Figure 3: Exposure-response curves of the relationships between long-term ozone exposure and mortality due to overall cardiovascular diseases (A), ischaemic heart disease (B), and stroke (C)
The solid red lines represent the effect estimates and the shaded area represents 95% CIs.

Discussion

To our knowledge, this is the first nationwide cohort study to investigate the effects of long-term ozone exposure on mortality in China, the most populous middle-income country. We consistently found that long-term ozone exposure was significantly associated with elevated risks of mortality from overall cardiovascular diseases and ischaemic heart disease, whereas the evidence for stroke mortality was comparatively weaker. The effect of ozone was more prominent in people aged 65 years and older than in those younger than 65 years. Furthermore, we observed an almost linear relationship between ozone concentrations and the risk of cardiovascular mortality.

Almost all studies investigating the chronic effects of ozone have been done in high-income countries, such as the USA and Canada. In the US Cancer Prevention Study II cohort,[9] the US NIH-AARP Diet and Health cohort,[10] and the Canadian Census Health and Environment Cohort (CanCHEC) study,[17] researchers found a significant and positive association between long-term ozone exposure and cardiovascular mortality. In these studies, a 10 ppb increase in warm-season ozone concentration was associated with a 1–4% increase in the risk of cardiovascular mortality (I00–I99), and the results were robust after adjusting for other air pollutants. We observed a similarly significant association in China, although the effect estimate in our study was larger. Notably, the chronic effects of ozone on cardiovascular mortality were not consistent in previous studies. Unlike the present study, two cohort studies in California, USA, did not find elevated risks of cardiovascular mortality corresponding to ozone exposure, even in single-pollutant models.[18,19] Paradoxically, a few studies found seemingly beneficial effects of ozone. For example, in a Danish cohort[20] and an English cohort,[7] long-term ozone exposure was estimated to be negatively associated with cardiovascular mortality. The inconsistency in the epidemiological findings of the cardiovascular effects of ozone might be attributable to many factors, such as the accuracy of exposure estimation, duration of follow-ups, population characteristics, and levels of ozone exposure. Therefore, more evidence from prolonged and large-scale cohort studies is urgently needed to better understand the chronic effects of ozone on the cardiovascular system.

After adjusting for $PM_{2.5}$, we found a significant and robust association between long-term ozone exposure and mortality due to ischaemic heart disease (HR 1·170 [95% CI 1·051–1·302]). Consistently, in the NIH-AARP Diet and Health Study, Lim and colleagues[10] showed a positive association between ozone and ischaemic heart disease mortality (HR 1·05 [95% CI 1·03–1·08] per 10 ppb increase). The CanCHEC study similarly suggested that ozone exposure was significantly associated with mortality due to ischaemic heart disease (HR 1·06 [95% CI 1·04–1·08] per 9·5 ppb increase).[17] However, our estimates of the effect of ozone on stroke mortality should be treated with caution, as the association lost statistical significance after adjustment for $PM_{2.5}$, possibly due to diminished statistical power and increased statistical uncertainty caused by a relatively high correlation between $PM_{2.5}$ and ozone (r=0·77). Thus, we cannot confirm an independent effect of ozone on stroke mortality—a finding consistently observed in most, but not all, previous studies done in high-income countries. For example, the US Cancer Prevention Study II cohort,[9] the NIH-AARP Diet and Health Study cohort,[10] and the California Teachers Study cohort[18] did not observe prominent effects of ozone on stroke mortality, whereas a cohort study in Canada estimated a statistically significant effect.[21] These findings suggest that ischaemic heart disease might be one of the primary causes of ozone-related cardiovascular mortality.

Although the exact biological mechanisms by which ozone exposure contributes to cardiovascular mortality remain uncertain, some studies have proposed a few plausible mechanisms. For example, inflammatory cytokines that are initially produced in the respiratory tract following ozone inhalation have the potential to enter the circulatory system and trigger a systemic

inflammatory response,[22,23] which might consequently lead to the onset or exacerbation of cardiovascular diseases. Exposure to ozone can also stimulate the release of biomarkers related to coagulation, platelet dysfunction, and endothelial injury.[24,25] Over time, these changes might increase the potential for thrombosis and then promote ischaemic heart disease or thromboembolic diseases. Moreover, studies have shown that ozone exposure might lead to onset of cardiovascular disease by modulating the autonomic nervous system and neuroendocrine system.[26,27] However, we noted that not all studies exploring biological mechanisms identified a mechanistic basis for the cardiovascular effects of ozone described in epidemiological studies.[28]

In subgroup analyses, we observed that people aged 65 years and older might be more vulnerable to cardiovascular mortality due to ambient ozone pollution than those younger than 65 years. Age has been shown to be of the most common demographic characteristics that increases susceptibility to short-term ozone exposure,[29] although there is no evidence for this observation in long-term exposure studies. In the NIH-AARP Diet and Health Study cohort in the USA, Lim and colleagues[30] also found that the effect estimate for ozone and cardiovascular mortality was slightly larger in old people than in young people, but the between-group difference was insignificant.

Evaluating the shape of the exposure–response function between ozone exposure and the risk of cardiovascular mortality is crucial for estimating the disease burden of ozone and revising air quality guidelines for ozone. In line with a previous study,[10] we observed a continuous upward trend in the risk of cardiovascular mortality as warm-season ozone concentrations increased from approximately 55 μg/m³ to 120 μg/m³. There is no obvious safe threshold for these relationships, which supports the updated WHO air quality guidelines (ie, a peak season average for ozone of 60 μg/m³).

Some uncertainty in effect estimations should be noted. First, we used ambient ozone concentrations as a proxy for individual exposure, which could lead to exposure misclassification as participants spent most of their time indoors. We assigned the predicted ozone concentrations to each participant's residential address at baseline, as residential information was unavailable during the follow-up period, which could lead to exposure measurement errors. However, we do not think this could substantially affect our results, as frequent relocation is not common in Chinese culture. Previous studies also revealed a minimal impact on the associations between lifetime or long-term exposure and mortality when residential mobility was not considered.[17,30] Moreover, due to the scarcity of ground-level ozone measurements before 2013, we used exposure prediction models to simulate ozone concentrations, which might also have introduced uncertainty. Second, some degree of under-reporting might exist in the death registration system, as in almost all registration databases. However, we believe the under-reporting rate is acceptable since reporting of deaths is mandatory in China and a series of quality control or assurance measures are in place to ensure reporting of deaths. Moreover, the DSP system has been used in various governmental or international reports and publications. Third, we did not adjust for the possible confounding effects of other gaseous pollutants because of the scarcity of such data.

In summary, this cohort study is, to the best of our knowledge, the first to evaluate the cardiovascular effects of long-term ozone exposure in China, a middle-income country, and to depict exposure–response curves over a relatively wide range of ozone concentrations. Our study found a clear association between long-term ozone exposure and an increased risk of mortality from cardiovascular diseases, especially ischaemic heart disease. These findings, combined with existing evidence, could help to establish a more precise exposure–response function for future disease burden estimation and also suggest that a peak-season standard for ambient ozone concentrations, in addition to the current 8h and 1h standards, is needed in China.

Contributors
YN and YZ did the statistical analysis and drafted the manuscript. PY collected the health data; XM, WW, and CL developed exposure prediction models; MZ and HK had full access to all the data in the study; all authors accessed and verified the underlying data. RC, JSJ, and YQ revised the manuscript critically. HK and MZ designed the study and gave final approval of the version to be published. HK and MZ had final responsibility for the decision to submit for publication.

Declaration of Interests
We declare no competing interests.

Data sharing
The exposure and health data used in this study are available on request via email from the corresponding authors.

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