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Long-term exposure to ozone and diabetes incidence: A longitudinal cohort study in China

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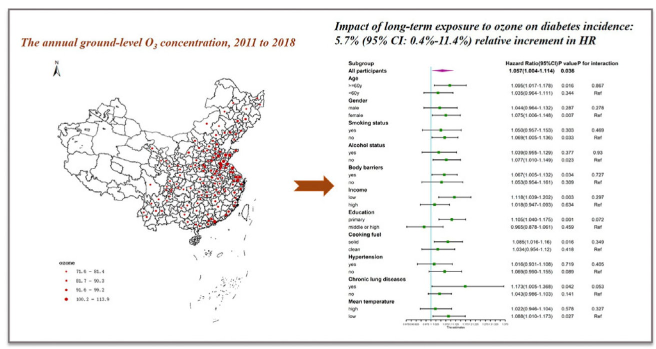
HIGHLIGHTS

- This is the first prospective cohort study to estimate the association between long-term exposure to O_3 and diabetes incidence in China.
- Long-term ozone exposure is positively associated with higher hazard ratio of diabetes occurrence.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Ozone (O_3) has become a prominent air pollutant problem as other pollutants concentrations have decreased obviously since China published Air Pollution Action Plan Pollution Prevention Action Plan in 2013. Few studies examined the association between O_3 and diabetes especially in developing countries. This study was designed to investigate the above topic in China.
Methods: We conducted a prospective cohort study based on a nationwide survey of 13,548 adults from China Health and Retirement Longitudinal Study. City-level exposure to ozone for each participant was matched through ChinaHighO_3 dataset. Time-varying cox proportional hazard regression model was applied to determine the association. Stratification analyses were conducted to explore potential effect modification.
Results: The annual mean concentration of O_3 was 86.6 μg/m^3. A 10 μg/m^3 increase in 1-year average O_3 concentration was associated with 5.7% (95% CI: 1.004–1.114) relative increment in hazards ratio of diabetes incidence in the fully adjusted model. Results stayed stable when controlling for physical activity, $PM_{2.5}$ and mean temperature.
Conclusions: Our findings provided initial support for a positive and robust association between long-term exposure to O_3 and diabetes incidence in a developing country. More scientific and social attention should be attached to the ozone-induced risks of diabetes occurrence.

1. Introduction

Driven by clean air policies (China's Air Pollution Action Plan Pollution Prevention Action Plan published in 2013), the air quality in China has improved rapidly since 2013 (Xue et al., 2021). The annual average concentrations of $PM_{2.5}$, PM_{10}, SO_2 and CO decreased in the 74 key

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cities. However, no significant change was seen in annual average concentrations of ozone (20.4% increase; 95% CI: -30.1-7.0) (Huang et al., 2018). For a long period of time in the future, O_3 will become a prominent problem that affects ambient air quality after PM_{10} and $PM_{2.5}$. Ozone is an important trace and greenhouse gas in the atmosphere yet and it can elicit a wide range of adverse effects on human health. Epidemiologic and experimental studies have proved that higher and worsening O_3 pollution especially in densely populated areas of China does harm to pulmonary function disorder, respiratory disease hospital admission, induction and exacerbation of asthma, and risks for diabetic deaths (Berman et al., 2012; Mustafic et al., 2012; Parrish et al., 2012; Turner et al., 2016; Vinikoor-Imler et al., 2014).

Diabetes is a major risk factor for morbidity and mortality worldwide (Roglic and Unwin, 2010). The past two decades have witnessed a concerning rise in the incidence of diabetes (Bragg et al., 2017). Air pollution has accounted for nearly 40% of all studies that explore environmental determinants of diabetes (Dendup et al., 2018). Among them, there existed published literature reporting that air pollution is a contributor to the risk and progression of diabetes, especially type 2 diabetes (Eze et al., 2015). A meta-analysis reviewing 17 studies found significant associations between six air pollutants (PM_{10}, $PM_{2.5}$, NO_2, O_3, sulphate and SO_2) and diabetes with pooled relative ratios or mortality risk ratios ranging from 1.01 to 1.07 per 10 μg/m^3 increases in pollutants (Janghorbani et al., 2014), while no study focused on ozone was conducted in Asia. Moreover, only 2 cross-sectional studies in the included literature examined the association between long-term exposure to traffic-related pollutant and diabetes. Evidence on the long-term effect of ozone was lacked. Briefly, most published papers were from the North American and Western European populations (Eze et al., 2015; Janghorbani et al., 2014; Wang et al., 2014), associations between O_3 exposure and diabetes have been scarcely studied in developing countries. Notably, east Asian populations (e.g., China) were different in their risk profile for diabetes compared with American and European populations (Hu and Jia, 2018; Kodama et al., 2013). To sum up, China, known for the highest prevalence of diabetes worldwide and high ozone pollution, is in urgent need to investigate the association between long-term ozone exposure and diabetes incidence (Dzhambov, 2018).

Among the existed original studies concentrated on the long-term exposure to ozone and diabetes, 33-communities study by Yang comprehensively explored the associations of long-term exposure to ozone with diabetes prevalence (Yang et al., 2018), but its cross-sectional design made it difficult to establish a causal association and the study samples only covered 5 cities in Liaoning province lack of representation. The cohort study in 105 United States cities reported positive association between long-term ozone exposure with a hazard ratio for mortality of 1.07 (95% CI: 1.05–1.10) for diabetes (Zanobetti and Schwartz, 2011). Liu et al. reported no significant association between long-term exposure to O_3 and type 2 diabetes prevalence (Liu et al., 2016), while a cohort study of African American women indicated the opposite result for incident diabetes (Jerrett et al., 2017), which showed inconsistent results. Besides, the concentration of long-term ozone ranged from 26.6 to 71.4 μg/m^3 in the above studies which was below the annual level in China.

Our study aims to provide population-based evidence on the association between long-term exposure to ozone based on a longitudinal cohort in China. We further test the modification effect of a variety of factors including personal characteristics, comorbidities and area-level environmental variables. Nowadays, public health policies on the environmental issues are made under uncertainty, especially when prevention is better than cure for chronic non-communicable diseases. The public health implication of our study is to provide scientific evidence of potentially detrimental metabolic effects of air pollution which should be communicated with stakeholders. The evidence of detrimental metabolic effects of ozone would lend further support to public health issues on the control of ozone pollution and prevention of diabetes.

2. Methods

2.1. Study population

The study population was from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS was launched in 2011, covering 150 counties, 450 villages, and about 17,000 individuals in 10,000 households. Follow-ups have been conducted in 2013, 2015, and 2018. A set of questionnaires on demographics, health status and function, behavioral habits and socio-economic information aimed to collect high-quality data representing the families and individuals of middle-aged and elderly people aged 45 and above in China. The subjects aged 45 years or more and recruited from baseline of cohort in 2011 to the first occurrence of diabetes or end of follow-up were included so that we used the data of fixed cohort to the analysis. 13,548 individuals were included from 27 provinces, municipalities, and autonomous regions, 123 cities and autonomous prefectures in China. The flowchart of study participants recruitment in the analysis was shown in Fig. A.1.

2.2. Estimation of air pollution and meteorological factors

We collected the ozone data from ChinaHighO_3 dataset, which generated from OMI Total-column O_3 products together with other auxiliary data (e.g., ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations) using artificial intelligence by considering the spatiotemporal heterogeneity of air pollution (Wei et al., 2021; Wei et al., 2022). The data we obtained was the OMI Level 3 (L3) yearly 0.25 degree (≈25 km) gridded ground-level O_3 concentration measurements in China from 2010 to 2017, averaged from the Level 2 daily (local time 13:30) products (Wei et al., 2021; Wei et al., 2022). This dataset had high accuracy with a cross-validation coefficient of determination (CV-R^2) of 0.84 and a root-mean-square error (RMSE) of 20.11 μg/m^3 on a daily basis. Annual $PM_{2.5}$ concentrations and trends using advances in satellite observations, chemical transport modeling, and ground-based monitoring $PM_{2.5}$ data was extracted from research output by Hammer and his colleagues (Hammer et al., 2020). The resultant annual mean geophysical $PM_{2.5}$ estimates are highly consistent with globally distributed ground monitors (R^2 = 81%; slope = 0.90). Temperature data was obtained from the China Meteorological Data Sharing Service System.

The effects of exposure to O_3 on diabetes incidence were modeled as time-varying variables, as it may be more informative to have long-term ozone measurements before the survey for several years. Specifically, we merged the grid cells of the 0.25-degree gridded ground-level O_3 products over the study period with the boundaries of China's administrative divisions, with individuals who resided in the same city sharing the same exposure levels. The modeled exposures were recorded as city-level averages and we calculated the one-year average concentrations before the year of outcome occurrence or end of follow-up as indicators of the long-term exposure. Similarly, we estimated 1-year average city-level concentration of $PM_{2.5}$ and temperature as measurements into the models.

2.3. Diabetes definition

Incidence cases of diabetes were confirmed by self-report of doctor diagnosed diabetes or high blood sugar during 3 waves of follow-up according to the questionnaire. The prevalence of diabetes during 2011 and 2018 was 11.5%, which was in line with the latest data (11.2%) reported in a large national cross-sectional survey during 2015 and 2017 including 75,880 adults ≥18 years old in China (D. B. o. C. M. Association, 2021; Society, 2021). Thus, we believed that our study population was representative of the Chinese population aged 45 years or older.

We did additional sensitivity analyses using different definitions of diabetes. According to the recommendations of the American Diabetes Association and Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2020) (A. D. Association, 2013), the glycosylated hemoglobin (HbA1c) was used as supplemental indicator of diabetes. Unlike fasting and postprandial blood glucose that reflect immediate blood glucose levels, HbA1c reflects the subject's blood glucose control during the past 2 to 3 months. Therefore, HbA1c is considered to be the gold standard for assessing the long-term blood glucose control level and the management of diabetes. As we aimed to evaluate the long-term impact of ozone exposure, self-reported diabetes, and/or HbA1c ≥6.5% were selected as diagnosis definition in the sensitivity analysis. Due to the data availability of blood tests, sensitivity analysis could merely be conducted with data from 2011 and 2015.

2.4. Statistical analysis

We fit time-varying cox proportional hazard regression models and estimated hazard ratios (HR) and 95% confidence intervals (CI) to assess the association between long-term exposure to ozone and diabetes incidence per 10 μg/m^3 increment. Time-varying effect emerges when the proportional hazards assumption is not fulfilled. So, to identify time-varying coefficients is actually to test the proportional hazards assumption after fitting a Cox proportional hazard model (Zhang, 2017). The proportional hazards assumptions were assessed by analyzing Schoenfeld residuals. The time varying coefficient can be described with a step function or a parametric time function through time-varying cox proportion hazard regression models (Zhang, 2017).

The analyses began with a basic model adjusted for age, gender and health-related factors. Health-related factors included smoking status, alcohol status, disability, social activity and body barriers. Prior comments pointed out that high concentrations of air pollution might inhibit the opportunities for outdoor recreation, social interaction, and commuting or leisure time, thereby raising the risk of diabetes (Dzhambov, 2018). Also, walkability may influence the incidence of diabetes so that social activity and body barriers were included in the basic model. Model 2 was based on model 1 plus social-economic factors which included household income, education and cooking fuels. Additionally, model 3, the fully-adjusted model contained the covariates in model 2 and comorbidities including hypertension, chronic lung diseases, liver diseases and stomach or digestive diseases which shared similar behavioral and dietary patterns with low physical activity, smoking, alcohol consumption and high fat or sugar intake diet in contrast with diabetes. Adjusting for these covariates, we were able to perceive the potential confounding effect of the unmeasured individual risk factors.

We assigned data from CHARLS to each study participant for the predicted concentrations of household annual income. Self-reported data on age, gender, smoking status, alcohol status, disability, social activity and body barriers were obtained at baseline in 2011. Hypertension, chronic lung diseases, liver diseases and stomach or digestive diseases were time-varying variables considered as comorbidities in the year of outcome diagnosis. Among them, all the variables were categorized into the stratification analyses except age as the continuous variable (converted to categorical variable with 60 years in the stratification analyses). Given earlier findings on modification effects of nitrogen dioxide and temperature on the health effect of ozone (Jerrett et al., 2017; Turner et al., 2016), we further estimated the effect under different $PM_{2.5}$ and mean temperature levels.

To test the robustness of the association, we subsequently added several variables into the sensitivity analysis of three models including body mass index (BMI), physical activity, the co-pollutant $PM_{2.5}$ and mean temperature, as potential confounders. BMI and physical activity could only be in the sensitivity analysis due to the incompleteness of information for most of the participants.

All analyses were performed using 'survival' package in R 4.1.0 with a priori α level of 0.05 to determine statistical significance.

3. Results

We recruited 13,548 individuals to the study which was composed of adult participants with an average age of 59.0 years (SD: 9.5) and a roughly equal sex distribution (male:female=1:0.9). 1209 incident cases appeared during 7-year follow-ups and the incidence of diabetes in the study population was 8.9%, which generally corresponded to the results from a multi-level spatial analysis of data from 98,058 adult subjects based on 2010 China Chronic Disease Surveillance Report (8.3%–12.7%).

Table 1 summarizes the characteristics of the study population and diabetes incidence in the CHARLS Longitudinal Study cohort. 37.6% of participants had smoke history and 42.0% had alcohol assumption. There existed 625 individuals with obesity and 64.5% with difficulty to walk 100 m. Co-existing comorbidities were found in 14.3% of study population with hypertension, 6.9% with chronic lung diseases, 3.2% with liver diseases and 9.0% with stomach or digestive diseases. Fig. 1 illustrates the annual ground-level O_3 concentration in the CHARLS Longitudinal Study during 2011 and 2018. The average air pollution exposures from 2011 to 2018 were 86.6 μg/m^3 for O_3 and 45.0 μg/m^3 for $PM_{2.5}$. The annual mean temperature was 15.04 °C. On average, the O_3 exposure level was 89.5 μg/m^3 among diabetes patients, slightly higher than that among non-diabetes patients (86.5 μg/m^3).

For diabetes per 10 μg/m^3 increase in O_3, we observed positive associations of diabetes with long-term exposure to ozone in three models. The hazard ratio of incident diabetes increased by 7% over a 10 μg/m^3 increment (95% CI: 1.018–1.125). After controlling for social-economic factors, the effect estimate decreased slightly but still held statistical significance (HR = 1.066, 95% CI: 1.013–1.121). The HR estimate still had a tiny decline to 1.057 (95% CI: 1.004–1.114) in the fully adjusted model additionally controlling for 4 comorbidities. With further control for BMI), the effect was reduced in model 1 and 2, while lost statistical significance in model 3. Regarding the physical activity, there was no indication of change of results in each model. When including $PM_{2.5}$ and mean temperature into the model, the HR estimates stayed relatively stable shown in Table 2.

Fig. 2 demonstrates a forest plot of effect modification of the association between ozone exposures and incidence of diabetes in the

Table 1
Characteristics of the study population and diabetes incidence in the CHARLS Longitudinal Study cohort.

Characteristics	Level	Total (N = 13,548)	Cases	Incidence (%)
Age (mean (SD))	Overall	59.0 (9.5)	1209	8.9
Gender (n, %)	Female	7017 (51.8)	720	10.3
	Male	6531 (48.2)	489	7.5
Smoking status (n, %)	Current or ever	5089 (37.6)	369	7.3
	Never	8459 (62.4)	840	9.9
Alcohol status (n, %)	Frequent or rare	5688 (42.0)	439	7.7
	Never	7860 (58.0)	770	9.8
Income (n, %)	High	6853 (50.6)	616	9.0
	Low	6695 (49.4)	593	8.9
Education (n, %)	Primary	9222 (68.1)	828	9.0
	Middle or high	4326 (31.9)	381	8.8
Cooking fuels (n, %)	Solid	7455 (55.0)	682	9.1
	Clean	6093 (45.0)	527	8.6
Disability (n, %)	Yes	2334 (17.2)	233	10.0
Social activity (n, %)	Yes	6327 (46.7)	569	9.0
Body barriers (n, %)	Yes	8744 (64.5)	882	10.1
Obesity (n, %)	Yes	625 (4.6)	123	19.7
Hypertension (n, %)	Yes	1944 (14.3)	425	21.9
Chronic lung diseases (n, %)	Yes	933 (6.9)	136	14.6
Liver diseases (n, %)	Yes	432 (3.2)	75	17.4
Stomach or digestive diseases (n, %)	Yes	1217 (9.0)	233	19.1

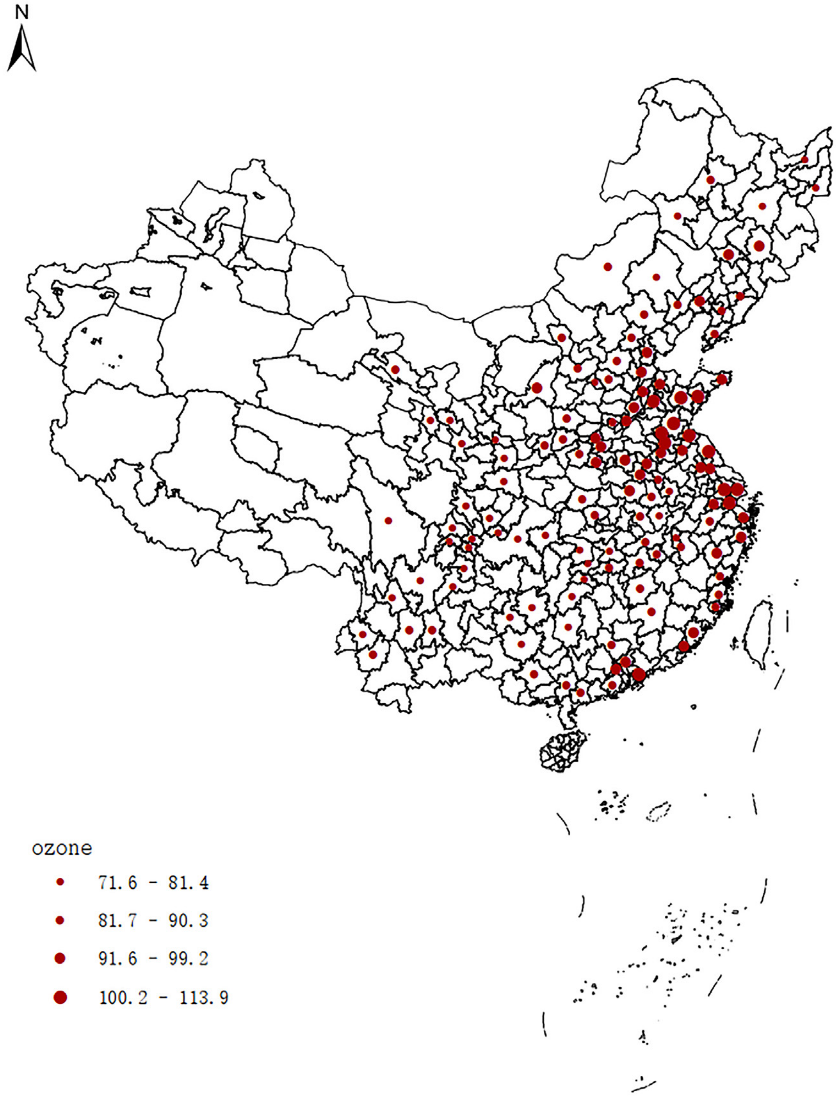

Fig. 1. The annual ground-level O_3 concentration in the CHARLS Longitudinal Study during 2011 and 2018.

CHARLS Longitudinal Study cohort. Although a stronger relationship was also found in some subgroup, no significant difference was observed. We discovered that the increase in diabetes hazards was greater for the elderly (>60 years) and women. When stratified for health-related factors and social-economic factors, the association for ozone was mainly higher for the non-smokers, non-drinkers, participants with body barriers, participants with low income level or low education status, participants using solid cooking duels. Those diagnosed with chronic lung diseases, without liver disease and stomach or digestive disease, O_3 also showed higher effect estimate. We further estimated the effect modification of $PM_{2.5}$ and mean temperature, and the results revealed a greater relationship when the mean temperature was below the median (HR = 1.088, 95% CI: 1.010–1.173). Plus, the effect estimate was stronger in the high $PM_{2.5}$ level compared to low $PM_{2.5}$ level (HR = 1.066, 95% CI: 1.012–1.122) with no between-group significance.

Additional sensitivity analyses based on several different definitions for diabetes generated similar relative ratio around 1.1 (Table A.2). Both results from cross-sectional study in 2011 or 2015 and longitudinal study from 2011 to 2015 reported robust association between ozone exposure and diabetes incidence. For example, when self-reported diabetes and/or HbAlc ≥ 6.5% were considered as definitions of outcome, the prevalence was 14.9%, comparable to previous study (p = 15.8% in Kan's study (Liu et al., 2016), p = 10.9% in Yang's study (Yang et al., 2018)). The relative ratio of diabetes was 1.063 (95% CI: 1.002–1.127), which stayed consistent with the results in main analysis.

4. Discussion

To our knowledge, this has been the first longitudinal cohort study to date to investigate the associations of ambient ozone pollution with diabetes in Asia. Significant and robust associations of long-term exposure to O_3 with diabetes incidence in China were observed. In conclusion, we believed that chronic effect of ambient ozone exposure could contribute to diabetes formation.

So far, the published review indicated positive pooled estimates about the impact of air pollutants on diabetes risk (Eze et al., 2015; Janghorbani et al., 2014). Our results were in accordance with previous reviews. A 4.9% increase of the pooled risk ratio or mortality risk ratio of diabetes associated with O_3 was estimated (95% CI: 1.018–1.081) summarized by Janghorbani et al. (2014). The prospective analysis in a large cohort of African American women reported a HR of 1.18 (95% CI: 1.04–1.34) per 6.7 ppb increase of ozone (Jerrett et al., 2017). Relevant studies conducted in Rome assessing the association between long-term exposure to O_3 and occurrence of type 2 diabetes also proved a significant effect (1.015, 95% CI: 1.002–1.027) per 10 μg/m^3

Table 2
Association between ozone exposure and incidence of diabetes in the CHARLS Longitudinal Study. HR and 95% CI per 10 μg/m^3 increment.

	HR	95% CI	p value
Model 1	1.070	1.018–1.125	0.008
+BMI	1.061	1.009–1.115	0.021
+Physical activity	1.070	1.018–1.125	0.008
+$PM_{2.5}$	1.072	1.019–1.128	0.007
+Average temperature	1.068	1.016–1.123	0.010
Model 2	1.066	1.013–1.121	0.014
+BMI	1.057	1.005–1.112	0.032
+Physical activity	1.066	1.013–1.121	0.014
+$PM_{2.5}$	1.068	1.015–1.123	0.012
+Average temperature	1.064	1.012–1.119	0.016
Model 3	1.057	1.004–1.114	0.036
+BMI	1.052	0.999–1.109	0.056
+Physical activity	1.057	1.003–1.114	0.037
+$PM_{2.5}$	1.056	1.003–1.113	0.040
+Average temperature	1.057	1.003–1.114	0.037

Model 1: Basic model, adjusted for age, gender and health-related factors. Health-related factors included smoking status, alcohol status, disability, social activity and body barriers.
Model 2: Model 1 plus social-economic factors. Social-economic factors included income, education and cooking fuels included solid or clean fuels.
Model 3: Fully adjusted model, model 2 plus comorbidities. Comorbidities included hypertension, chronic lung diseases, liver diseases and stomach or digestive diseases.
Abbreviations: HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.
Note: Categories for variables were dichotomized: gender (male or female); smoking status (yes: current or ever; no: never); alcohol status (yes: frequent or rare; no: never); disability (yes or no); social activity (yes, no or missing); body barriers (yes or no); BMI (with obesity: >30, according to WHO definition; without obesity: ≤30); income (low: below median; high: above median); education (low: illiterate or primary; high: middle or high); cooking fuels (solid: coal or firewood; clean: electricity, solar power or natural gas); comorbidities (yes, no or missing); $PM_{2.5}$ (low: below 10 μg/m^3; high: above 10 μg/m^3, according to WHO guideline value).

increment (Renzi et al., 2018). Besides, the cross-sectional study in 33-communities China Health Study provided evidence of a positive association between long-term exposure to O_3 and incident diabetes that the adjusted OR per 22 μg/m^3 increment was 1.14 (95% CI: 1.05–1.25) (Yang et al., 2018). Our study detected a 7% increase in the basic model and a 5.7% increase in the fully adjusted model (95% CI: 1.004–1.114) per 10 μg/m^3 increment of O_3. The magnitudes were comparable to prior studies. In sum, chronic diabetogenic effect of ozone exposure could be implied according to the overall evidence.

The biological mechanism behind depended on multiple evidence. Animal experiments suggested that O_3 exposure may also have the capacity to induce metabolic insulin resistance. For instance, sub-acute exposure to O_3 for 4 days developed elevations in fasting glucose levels and rats' body insulin resistance (Vella et al., 2015). Scholars additionally pointed out the hypothesis that air pollution would lead to heavy oxidative stress and adipose tissue inflammation resulting in endoplasmic reticulum stress, insulin signaling abnormalities and apoptosis, which might insulin resistance (Andersen et al., 2012; Fleisch et al., 2014). Plus, O_3 could cause adverse systemic metabolic responses via activation of the sympathetic nervous system, by hypothalamic inflammation or both (Bass et al., 2013).

In the stratified analysis, we did not find an effect modification for any variable as no significant difference was observed between the subgroups. Nevertheless, the effect estimate was significant in one subgroup and the subgroup result gave enlightenment to the identification of sensitive population. Effects were enhanced in the elderly (>60 years), showed discrepancy with previous result of age-stratified analysis in Yang's study and Renzi's study (Renzi et al., 2018; Yang et al., 2018). Yang's study concentrated on six pollutants except for ozone and Renzi's study was conducted in Rome where the IQR of

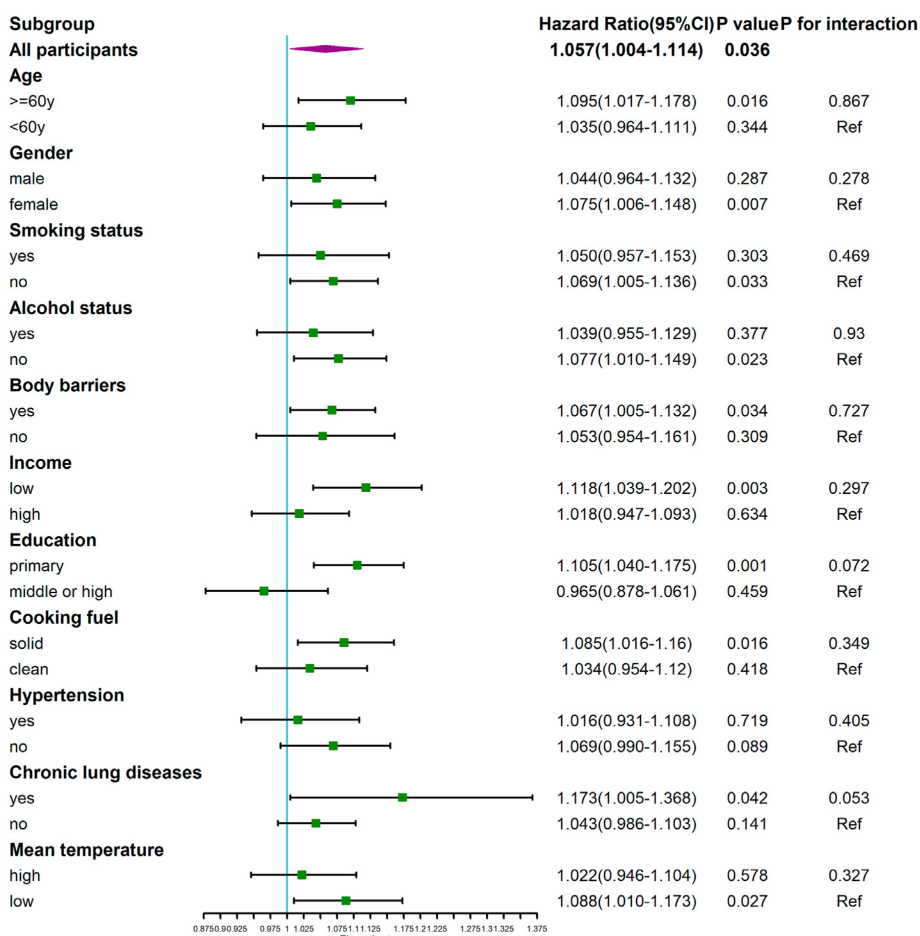

Fig. 2. Forest plot of effect modification of the association between ozone exposures and incidence of diabetes in the CHARLS Longitudinal Study cohort. HR and 95% CI per 10 μg/m^3 increment.

O_3 was 5.5 μg/m^3 (17.7 μg/m^3 in our study). Besides, the female, the nonsmokers and nondrinkers showed higher effect estimates, consistent with existed literature (Andersen et al., 2012). Actually, the smoking pattern showed a large difference between women and men, with most smokers being men (Wang et al., 2018). The adverse effect of smoking on the respiratory system may, to some extent, mask that of air pollution among men. In addition, men spent more time working outside and were more exposed to ambient air pollution so the different time-activity patterns might have a key role in the observed difference.

The associations for ozone with diabetes were generally stronger in the subjects who were less educated and possessed lower income lack of statistical significance. People with low levels of education and income were more likely to have chronic diseases and limited access to health services (Kan et al., 2008). Furthermore, enhanced air pollution effects were not seen with higher BMI. The diabetes risk factors accumulated with advancing BMI and obscured the effect of ozone in population with obesity. Those who without obesity would be more affected by O_3 exposure. Last but not least, the prevalence of diabetes among the obese groups was much higher than the subjects without obesity so the obese groups were more likely to use anti-diabetes medication, which might attenuate the glycaemic effect of air pollutants. Notably, the sub-population with chronic lung diseases also showed stronger relationship between ozone and diabetes, in accordance with similar study (Renzi et al., 2018), which was in biologically plausible. As Rao et al. asserted that long-term exposure to ozone may induce diabetes through similar pathways as $PM_{2.5}$ that the pollutant may lead to oxidative stress in the lungs if sustained over time, generating systemic pro-inflammatory and autonomic responses linked to adverse health outcome (Rao et al., 2015). Still, previous studies showed that chronic respiratory disease patients are more likely to live in areas with higher air pollution levels than the rest (Andersen et al., 2011; J. et al., 2011).

Cooking fuel was a representative of indoor pollution indicator. Solid cooking fuels included coal or firewood biomass burning, which may cause severe indoor air pollution. In the prior report, South Asia showed the highest regional concentration of ambient $PM_{2.5}$ from household cooking (8.6 μg/m^3) (Chafe et al., 2014). And $PM_{2.5}$ emissions from household cooking constituted an important portion of ambient $PM_{2.5}$ concentrations in many places including China (Chafe et al., 2014). Exposure to $PM_{2.5}$ impaired glucose and insulin tolerance through cardiometabolic pathways and lead to systematic pro-inflammatory and autonomic responses linked to adverse health outcomes such as diabetes if sustained over time (Rajagopalan et al., 2020). We also detected that the effect was greater under high $PM_{2.5}$ concentration level which proved the above discovery at the same time. Besides, the associations were stronger when the temperature was low although there existed no significance between two temperature levels. In the air health index study recently published by Zhang et al., the average daily percentage of excess mortality related to air pollution and non-optimum temperature was 28.23%, among which non-optimum temperature accounted for 23.47% (Zhang et al., 2021). Also, published literature pointed out that the cold effect occupied the main role in the adverse health effect of temperature (Gasparrini et al., 2015). Cold induces bronchoconstriction and suppresses mucociliary defences and other immunological reactions, resulting in local inflammation which may lead to adverse systemic metabolic responses (Gasparrini et al., 2015).

The present study held several strengths. First, this has been the first nationwide prospective cohort study to date to investigate the association of ambient ozone pollution and incident diabetes in China, which provided novel epidemiological knowledge on the hazardous effects of ozone exposure especially against the backdrop of increase in ambient ozone pollution concentration. Second, we added the mean temperature, indicators of walkability (disability and body barriers), indoor pollution (cooking fuels) and social interaction (social activity) to the analysis which corresponded to the advice proposed by previous remarks (Dzhambov, 2018) and confirmed the power of evidence.

Limitations also existed in our study. On the first hand, according to the unavailability of personal address information in the CHARLS Longitudinal Database, the air pollution measurement in our study was city-level and more precise estimation in prospective cohort study were warranted to avoid the exposure misclassification. On the other hand, the study cities were mainly located in the eastern region of China so that our results should be cautious to be generalized to overall populations in China. Plus, due to the characteristics of the database, the study population focused on the people over 45 years old so that the present discovery was mostly in connection with the middle-aged and elderly people. Finally, the residual confounding caused by area-level potential confounders like GDP, noise and green space may have an influence on the results. Nevertheless, our study was a prospective cohort study based on a nationwide database which provided a scientific basis for formulating and improving relevant policies so that it would have important implications for diabetes prevention and for public health protection, especially with the development of the increase of ozone concentration.

5. Conclusions

In conclusion, this prospective cohort study suggested that long-term exposure to O_3 might increase the risk of diabetes occurrence in China. Our findings demonstrated that ozone was an important modifiable environmental risk factor contributing to the incidence of diabetes in China. No significant difference was observed in the stratification analyses so that no susceptible populations could be determined. The evidence of detrimental metabolic effects of ozone should be heralded and communicated to stakeholders.

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CRediT authorship contribution statement

Yuxin Wang: Methodology, Software, Formal analysis, Writing – original draft. **Ru Cao:** Investigation, Methodology, Software. **Zhihu Xu:** Data curation, Software. **Jianbo Jin:** Conceptualization, Software. **Jiawei Wang:** Methodology, Visualization. **Teng Yang:** Visualization, Methodology. **Jing Wei:** Resources. **Jing Huang:** Conceptualization, Supervision, Methodology. **Guoxing Li:** Methodology, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.151634.

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